EFFECTS OF LONGTERM ANTIEPILEPTIC DRUGS ON VASCULAR RISK FACTORS AND ATHEROSCLEROSIS

Submitted in partial fulfillment of the requirements towards the conferment of

BRANCH - 1 DM NEUROLOGY

of

THE TAMIL NADU

Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

August 2013

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CERTIFICATE

This is to certify that the dissertation entitled **"EFFECTS OF LONGTERM ANTIEPILEPTIC DRUGS ON VASCULAR RISK FACTORS AND ATHEROSCLEROSIS"** is a bonafide original work of **Dr.L.A.RAVI**, in partial fulfillment of the requirements for D.M. Branch– I (NEUROLOGY) Examination of the Tamil Nadu Dr.M.G.R Medical University to be held in AUGUST 2013, under our guidance and supervision

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DECLARATION

I hereby solemnly declare that this dissertation titled **"Effects Of Longterm Antiepileptic Drugs On Vascular Risk Factors And Atherosclerosis"** was done by me in Institute of Neurology, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai -3, under the guidance and supervision of **Prof. Dr. S. Balasubramanian.MD., D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of D.M Degree Branch I (NEUROLOGY).

Place: Chennai
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ACKNOWLEDGEMENT

It gives me great pleasure to acknowledge all those who guided, encouraged and supported me in the successful completion of my dissertation.

First and foremost, I express my gratitude to, the **Dean Dr.V.Kanagasabai M.D.** for having permitted me to carry out this dissertation work at Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai.

I am extremely thankful to **Prof. Dr. K.Deiveegan, M.S., M.ch.,** Professor of Neurosurgery, Head of the department, Institute of Neurology, Rajiv Gandhi Government General Hospital Chennai for his constant encouragement, valuable guidance and support.

I express my deep sense of gratitude and sincere thanks to our respected and beloved Chief **Prof.Dr.C.Mutharasu, M.D., D.M., and Prof.Dr.S.Balasubramanian. M.D., D.M., Professor of Neurology,** Institute of Neurology, Rajiv Gandhi Government General Hospital, Chennai for their valuable suggestions, constant motivation, kind guidance and moral support without which this study would not have been possible.

I express my sincere thanks and gratitude to our Professors **Prof.Dr.K.Bhanu, DNB, D.M., Prof. Dr.R.Lakshmi Narasimhan, M.D., DNB., D.M.,** and **Prof.Dr.V.Kamaraj, M.D., D.M.,** for their valuable suggestions and support.

I express my sincere thanks and gratitude to our Professors **Prof.V.Sundar, M.Ch., Prof.S.Sundaram, M.S., M.Ch., Prof.K.Maheswar, M.Ch., Prof.S.D.Subbiah, M.Ch., Prof.S.Syamala, M.Ch., Prof.G.S.Jagan Narayana, M.Ch., and Prof.Ranganathan Jothi, M.Ch.,** for their valuable suggestions and support.

I am extremely thankful to our Assistant Professors **Dr.V.Ramakrishnan, D.M., Dr.P.Muthukumar. D.M., Dr.V.Kannan, D.M., Dr.S.Shanmugasundaram, DM.,** and **Dr.N.Shanmugasundaram, DM.,** for their valuable guidance and support.

I thank all Professors, Assistant Professors of Institute of Biochemistry, Department of Rheumatology and radiology for their valuable support in this study.

I owe my sincere thanks to all the patients and the technical staff who participated in the study for their cooperation which made this study possible.

CONTENTS

PROFORMA

EFFECTS OF LONGTERM ANTIEPILEPTIC DRUGS ON VASCULAR RISK FACTORS AND ATHEROSCLEROSIS

PATIENT INFORMATION:

SERIAL NO.

NAME: AGE ……. YEARS

GENDER: MALE/FEMALE MIN NO.

OP NO:

HEIGHT: cm WEIGHT: kg BMI-

ADDRESS: PHONE NO

Age of onset of epilepsy:

Duration of epilepsy:

Duration of AED:

Dosage of AED in mg/day

Average seizure frequency per month during previous 1 year;

HISTORY & PRESENTATION:

SEIZURE:

Description of ictus;

Post ictal state

TYPE OF SEIZURE:

1.Primary generalized(GTCS)

2.Focal with secondary generalization

3.complex partial

4.Absence

5.Myoclonic jerks

6.others

Average no. of seizure ……..over……..(day/week/month/year)

Idiopathic / Cryptogenic

Symptomatic :

Cluster attacks

Status epilepticus

Fever /Headache/Vomiting/

Limb Weakness

Sensory disturbance

Altered behavior

Trauma

Others:

PAST HISTORY:

Type of seizure-GTCS/simple/complex/absence/Myoclonus

Frequency……per…….

Number of years in remission(before current presentation)……yrs

Type of AED used in past –

1.PHT 2.PB 3.CBZ 4.Valproate 5.oxycarbamazepine 6.Others

Febrile seizure in childhood

Simple febrile/ Complex febrile seizure

ASSOCIATED CONDITIONS:

TIA/ CVA

Head injury

Surgery

Meningoencephalitis

Congnitive decline

COMORBIDITIES

DM / Hypertension / CAD /Stroke / Hyperlipidemia /Liver disease / Kidney disease

Rheumatological illness

Medications for systemic illnesses(with duration)

PERSONAL HISTORY

Alcoholism /smoking /tobacco chewing /

Diet Vegetarian / Non vegetarian

FAMILY HISTORY

Seizure /DM /HT / CAD /Hyperlipidemia

Others

EXAMINATION:

Temperature Pulse BP mmHg pallor

Icterus Lymphadenopathy Clubbing Pedal oedema

Carotid bruit Peripheral pulsation

Thyroid swelling

Neurocutaneous markers

CVS:

RS: ABDOMEN:

CENTRAL NERVOUS SYSTEM:

Sensorium:GCS : E V M

Meningeal signs:

HMF;

Cranial nerves:

Spino motor system:

CEREBELLAR Signs

Sensory:

0thers

LAB INVESTIGATIONS

Hb % gm%

TC

DC

ESR

Blood sugar

Blood urea

Serum creatinine

Electrolytes:

X ray CHEST

USG ABDOMEN

THYROID PROFILE:

CSF:

ECG

ECHO

EEG-

FASTING LIPID PROFILE

Total Cholesterol

LDL- C

HDL- C

Triglycerides

CRP:

CT BRAIN:

MRI BRAIN:

COMMON CAROTID INTIMA MEDIA THICKNESS(CCA-IMT)

RIGHT CCA IMT –

LEFT CCA IMT –

AVERAGE CCA IMT -

AEDs DETAILS:

DIAGNOSIS:

ABBREVIATIONS

AED	-	Antiepileptic drug
BMI	–	Body mass index
CBZ	-	Carbamazepine
CCA	–	Common carotid artery
CVD	-	Cardiovascular disease
CSWSS	-	Continuous spike and wave in slow wave sleep
CHD	-	Coronary heart disease
CNS	-	Central nervous system
CIMT	-	Carotid intima media wall thickness
CRP	-	C-reactive protein
EEG	-	Electroencephalography
GTCS	–	Generalised tonic clonic seizure
HDL- C	-	High-density lipoprotein cholesterol
LDL-C	-	Low-density lipoprotein cholesterol
MI	–	Myocardial infarction
PB	-	Phenobarbitone
PHT	-	Phenytoin
PRM	-	Primidone
ROS	-	Reactive oxygen species
TC	-	Total cholesterol
TGL	-	Triglyceride
VPA	-	Valproic acid
VSMCs	-	Vascular smooth muscle cells
WHO	-	World Health Organization

INTRODUCTION

Epilepsy is one of the most common disorders of the brain.[1] One of every ten people will have at least one epileptic seizure during a normal lifespan and a third of these will develop epilepsy. 50 million people are affected by epilepsy worldwide, accounting for 1% of the global burden of disease, equivalent to lung cancer in men and breast cancer in women.[2]

More than 30% of epileptic patients have to undergo longterm therapy with antiepileptic drugs.[3] Prolonged AED therapy is associated with several adverse effects such as metabolic disturbances, idiosyncratic reactions, behavioral or psychiatric problems and drug interactions.[4]

Risk factors for atherosclerotic events and cardiovascular disease include male sex, increased age, elevated plasma total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), decreased high-density lipoprotein cholesterol (HDL-C), CRP, high blood pressure, smoking and diabetes mellitus.[5-7]

Annegers et al[8] in their study have reported a high death rate due to ischemic heart disease and sudden cardiac death in symptomatic epileptic patients. But however a clarity on the issue of AED intake leading to cardiovascular mortality is not very clear. In this context there have been

few studies that have indicated that long term AED intake has been associated with increased vascular risk factors.

With this background the study of long term effects of antiepileptic drugs on vascular risk factors and atherosclerosis was conducted.

AIMS OF THE STUDY

1. To study the effect of antiepileptic drugs on vascular risk factors namely serum Lipid profile and CRP in epileptic patients.

2. To assess the effect of antiepileptic drugs on carotid intima media thickness, a marker of atherosclerosis in epileptic patients.

3. To assess the correlation between duration of the antiepileptic drugs, and carotid intima media thickness.

REVIEW OF LITERATURE

An epileptic seizure is a clinical event, which result from the synchronous and excessive discharge of a group of neurons in the cerebral cortex.

Epilepsy is the tendency to have recurrent, unprovoked seizures. Seizures can result from specific precipitants such as fever in young children; soon after stroke; metabolic disturbances. These seizures are termed acute symptomatic seizures. Following such seizures, the chance of an unprovoked seizure is usually quite low and so the person would not be considered as having epilepsy.

By this definition the incidence of epilepsy is 0.3–0.5% in different populations throughout the world, and the prevalence of epilepsy has been estimated at 5–10 persons per 1000.[9]

The classification of epilepsy:

While epilepsy is best considered a symptom of an underlying brain disorder, we can classify someone's epilepsy by aetiology, but this tells us very little about the clinical expression of the seizures, about the prognosis and about the expected findings on EEG. This information is contained within the classification of seizures and epilepsy. There is an

accepted international classification of seizures and epilepsy that is at present under revision. However, the basic concepts will be preserved.

The present International League against Epilepsy classification has a number of limitations, that it does not account for recent advances in genetics and neuroimaging.

Classification of seizures

The clinical manifestation of a seizure depends upon where in the brain it starts, and how far and fast it spreads. Seizures are divided into two broad categories: those originating from a localised cortical area are classified as partial (focal) seizures, and those characterized by initial synchronous discharges over both hemispheres are classified as generalised seizures.

Partial (focal) seizures

Sixty percent of focal seizures begins in the temporal lobes , with the remainder begins in the frontal lobes. Seizures originating in the parietal or occipital regions are relatively rare. Partial seizures are classified into three groups: simple partial, complex partial, and partial with secondary generalisation. Simple partial seizures are focal seizures in which consciousness is fully preserved. They are usually brief, stereotypical and intense, and their manifestation depends upon where the seizure begins. Common symptoms in temporal lobe epilepsy include:

d´ej`a vu, ‘butterflies’, fear, illusions and hallucinations (auditory, olfactory and gustatory) and complex visual hallucinations. In frontal lobe epilepsies, there can be focal jerking that can spread as a ‘Jacksonian March’, more complex motor posturing, a difficult-to-describe feeling in the head, and forced thinking. In occipital lobe epilepsy, there can be simple visual hallucination, usually coloured blobs in one part of the visual field. With parietal lobe epilepsies there can be focal sensory phenomena such as tingling that is sometimes painful, somatic illusions such as distortion of mouth or limb, or even sensations of vertigo.

Complex partial seizures are partial seizures with impaired consciousness. They can start as a simple partial seizure or the person may have impaired consciousness from the onset of seizure. In temporal lobe epilepsy, there may be motor arrest followed typically by chewing, lip smacking and swallowing (oroalimentary automatisms), and then fiddling with the hands (limb automatisms). Frontal lobe epilepsies can have more complex movements associated with them such as odd posturing (‘fencing posture’), large gestural movements such as pushing away, or rocking, as well as running, scissoring or cycling movements of the legs.

Generalised seizures:

The commonest of these are the tonic–clonic seizure and absence seizures, but there are also rarer seizure types. Generalised tonic–clonic seizures (GTCS; often termed convulsions) usually occur without warning, although sometimes they can be preceded by increasing frequency of another generalised seizure type, such as myoclonic jerks or absences. Initially the person is tonic (stiff) and may cry out (the 'epileptic cry'). The person will fall and may bite the side of the tongue as the jaw clenches. The person may also become cyanosed at this point. Clonic movements then begin, usually predominantly in the upper limbs. These are coordinated regular jerks that eventually slow and stop, at which point incontinence can occur. Most convulsions last less than 2 minutes. There is then a post-ictal period characterized by sleepiness and confusion lasting up to 20 minutes, but it may take longer for people to get over the full effects of the seizure (including lethargy, muscle aches, headache and a severely bitten tongue).

Typical absence seizures almost always begin in childhood or adolescence. There is motor arrest and staring. On occasions there can be fluttering of the eyelids, swallowing, and flopping of the head. The attacks usually last a few seconds, can occur many times a day and may be unrecognized, leading to a delay in diagnosis. There is immediate

recovery and no post-ictal phase. This seizure type is associated with a characteristic EEG of three-per-second generalized spike-and wave discharges. There are also atypical absences, which are usually part of more severe epilepsy syndromes associated with learning difficulties, such as the Lennox–Gastaut syndrome. In these the EEG is different, with slower and more irregular spike-and-wave discharges. Also the onset and cessation of the seizure is less clear and there are often additional features such as changes in body tone. Myoclonic seizures are sudden jerks that can involve a part of or the whole body.

They commonly occur in the morning within a couple of hours of waking in idiopathic generalised epilepsies Although they usually occur in more benign epilepsy syndromes, they can rarely be associated with devastating epilepsies with cognitive and neurological decline – the progressive myoclonic epilepsies. Not all myoclonus is epileptic and can even be physiological, for example sleep starts (hypnic jerks). Other generalised seizures consist of mainly atonic and tonic seizures. These are often termed ‘drop attacks’ and consist of sudden loss of body tone (atonic) or sudden increase in body tone (tonic), resulting in a fall. Recovery is generally rapid, notwithstanding any head injury.[10]

Classification of epilepsy syndromes

An epilepsy syndrome consists of a combination of clinical, seizure and EEG characteristics that make up a distinct entity. Diagnosis of an epilepsy syndrome has implications for prognosis and management. However, diagnosis of a particular epilepsy syndrome does not necessarily imply a single aetiology: many epilepsy syndromes are known to have multiple aetiologies. Some epilepsy syndromes are characterised by generalized seizures, others by focal seizures, and a few by both focal and generalised seizures. The first two of these can be considered generalised and focal epilepsy syndromes, respectively. Some epilepsy syndromes are always or nearly always idiopathic; others are always or nearly always symptomatic or probably symptomatic, but a number exist in idiopathic, probably symptomatic and symptomatic forms (e.g. West syndrome).

The term epileptic encephalopathy is used to denote epilepsies in which ongoing epileptic activity gives rise to progressive but potentially reversible neurological dysfunction which can be manifested as learning and behavioural problems or occasionally as motor problems. Only a very small number of epilepsies follow this pattern.

Febrile seizures

Febrile seizures are the commonest type of epileptic seizure occurring in 2–5% of the general population. They are epileptic seizures occurring in association with fever but without evidence of infection of the CNS, excluding those who have had previous non-febrile seizures or in whom there is a known cause of seizures. They usually occur between the ages of six months and six years. A family history is common. Most febrile seizures are GTCS, but other seizure types can be precipitated by fever, including tonic, clonic and myoclonic seizures. It is usual to classify febrile seizure as simple or complex.

Idiopathic generalised epilepsies

These are common forms of epilepsy occurring in childhood, adolescence and in adult life, and feature combinations of three seizure types: typical absences, myoclonic seizures and GTCS. In all of them a family history of epilepsy and of febrile seizures in infancy/early childhood is common.

EEG shows generalised discharges of spike and wave or of spikes/multiple spikes, the latter being characteristic of syndromes with myoclonic seizures. Despite reports of linkage to a variety of chromosome regions and of specific mutations in individuals and families, their genetic basis is still unclear.

Childhood absence epilepsy is common in 4years to 9 years of age group, girls are more affected than boys. It is characterised by typical absence seizures, usually lasting less than 20 seconds and occurring many times each day. The EEG is characterised by generalised 3-Hz spike-and-wave discharges. Response to appropriate medication is usually excellent, and most children become seizure free. The epilepsy commonly resolves, usually before age 12 years.

Juvenile absence epilepsy is similar to childhood absence epilepsy, but is rarer and usually starts in later childhood or adolescence. The typical absence seizures occur less frequently, but GTCS are common and occasional myoclonic jerks may also occur. Response to appropriate treatment is generally good, but the condition is likely to persist throughout adolescence and into adult life.

Juvenile myoclonic epilepsy is also common and probably under diagnosed. It usually begins between the ages of 10 and 18 years and has a genetic basis.

The epilepsy consists of early morning and/or late-evening myoclonic jerks, tonic–clonic seizures (in most) and absences (in a third). the condition is usually lifelong.

Benign myoclonic epilepsy of infancy is rare, usually starting between six months and three years of age. The predominant, often sole,

seizure type is myoclonic seizures occurring singly or inclusters. They may arise spontaneously or be provoked by noise or tactile stimuli.

Doose syndrome have myoclonic–astatic seizures; this starts in early childhood and is characterised by drop attacks caused by myoclonic seizures, atonic seizures (seizures characterized by a loss of muscle tone) or a combination of these seizure types (myoatonic seizures), and photically induced eyelid myoclonia with absences.

Benign childhood epilepsy with centro-temporal spikes, which is also known as **benign Rolandic epilepsy**, usually starts in mid to late childhood and is probably the commonest type of new-onset epilepsy in otherwise normal children in this age group. The seizures are focal and characterised by tingling and numbness of the lips and tongue, and twitching at the corner of the mouth. Seizures may spread, leading to impairment of consciousness and/or hemiclonic or GTCS. A majority of seizures occur in sleep, during which spread may be very rapid, such that the initial focal onset is not apparent. The EEG characteristically shows so-called centro-temporal spikes. Seizure remission is expected within a few years, and certainly before the age of 16 years.

Panayiotopoulos syndrome is also common, usually occurring in children of about four to six years of age. The seizures are characterized by autonomic symptoms, particularly nausea, retching and vomiting,

which usually begin in clear consciousness. Most seizures, however, progress with impairment of consciousness and sometimes hemiclonic and/or GTCS. Some seizures are mainly characterised by the child becoming flaccid and unresponsive. Characteristically the seizures are prolonged, often lasting over 30 minutes. A majority of the seizures occur in sleep and are very liable to be misdiagnosed. The EEG is characterised by multifocal spike-and-wave abnormalities. Total seizure count is usually low and remission is expected within a few years of onset.

EPILEPTIC ENCEPHALOPATHY:

West syndrome usually begins in the first year of life (peaking at three to nine months). The typical seizures are called epileptic or infantile spasms and consist of brief (up to a few seconds) episodes of contraction of truncal and limb uscles causing extension or flexion of the trunk and flexion or extension of the limbs. They may be quite subtle, particularly at onset. The seizures often occur in clusters, soon after awakening, on defecation or on feeding.

The EEG usually shows a characteristic pattern termed hypsarrhythmia. An identifiable cause can be found in around 90% of patients.

Structural brain abnormalities are common and can be genetic or acquired in origin. Tuberous sclerosis is the single commonest cause of West syndrome.

Some chromosomal abnormalities, including Down syndrome, are associated with a greatly increased risk of West syndrome. Occasionally West syndrome arises as a consequence of metabolic disorders, which may require specific treatments. Many children with West syndrome have developmental delay prior to onset of seizures. The onset of seizures is usually marked by developmental slowing, stagnation or regression, andmanychildren with the disorder will ultimately be diagnosed with severe learning difficulties. Up to20% eventually function within the normal range. This is more likely to be the case in those with idiopathic West syndrome. Epileptic spasms often subside after weeks, months or years. Some children remain seizure free but others develop other forms of epilepsy, including the Lennox–Gastaut syndrome.

Lennox–Gastaut syndrome is a rare epilepsy usually beginning in early–mid childhood and characterised by frequent seizures of multiple types including tonic and atonic seizures and atypical absences. Tonic–clonic, myoclonic and focal seizures may also occur.

Dravet syndrome usually begins after six months of life in a child who has been developing normally. Onset is typically with a febrile seizure, often prolonged with focal features, and may follow vaccination. Further similar seizures are likely over the next few months, some clearly febrile (but often low-grade fever), others during intercurrent illness without definite fever.

Usually in the second or occasionally third year of life the picture changes, with multiple seizure types developing. These may include myoclonic seizures, atypical absences, GTCS and focal seizures. Seizures often continue to be precipitated by fever and intercurrent illnesses. Accompanying the onset of this polymorphous epilepsy, developmental stagnation and even regression occurs and all affected children will eventually have severe learning difficulties, often with autistic behavioural problems. Motor problems, such as ataxia and spasticity, commonly develop. Eventually, often after some years, seizure frequency tends to reduce. The EEG is not particularly useful in the diagnosis, usually being normal early on. However, early photosensitivity is seen in a minority. Doose syndrome sometimes behaves as an epileptic encephalopathy, with around a half of those affected developing learning difficulties.

The **Landau–Kleffner syndrome** is a rare disorder usually occurring in previously normal children. It is characterised by a rather non-specific epilepsy (often mild) accompanied by regression in language and marked behavioural problems. Children developing it are often suspected of being deaf. It is usually accompanied by a characteristic EEG abnormality known as continuous spike and wave in slow wave sleep (CSWSS).

Similar problems can arise in children with other forms of epilepsy, with or without structural brain abnormalities, sometimes precipitated by AED medication.

Symptomatic/cryptogenic focal epilepsies

The symptomatic/cryptogenic focal epilepsies can occur at any age, and the seizure manifestation depends upon where in the cortex the seizure begins and how far and fast the seizure spreads.

Atherosclerosis:

Epidemiology of Coronary Heart Disease:

Cardiovascular disease (CVD) is the most frequent cause of premature death in both developed and in developing countries. The common form of CVD are stroke and coronary heart disease (CHD).

Risk Factors for Atherosclerosis:

Around one third of CHD and ischemic stroke in developed countries is related to increased body mass index (BMI) levels.[13] Risk of CHD is also directly related to blood cholesterol levels. Around 50% of CHD and ischemic stroke in developed countries is due to elevated total blood cholesterol levels.

Atherosclerosis

Atherosclerosis is a focal, inflammatory fibro proliferative response to endothelial injury. Russell Ross and colleagues proposed endothelial injury hypothesis 30 years ago.[14]

The normal artery wall is composed of two organized layers: intima and media. The intima is made up of a single layer of endothelial cells that are seated on basement membrane and then the internal elastic lamina . Beneath the IEL is the medial layer, comprising vascular smooth muscle cells (VSMCs) surrounded by basement membrane and embedded in interstitial extracellular matrix. The boundary of the media is marked by the external elastic lamina (EEL).

All infants have focal thickening of the coronary artery intima due to VSMC proliferation.[15] Although focal thickening is an important hallmark of the developing atherosclerotic plaque, this is considered to be an adaptive response to turbulent blood flow rather than pathological.

Endothelial dysfunction initiated by the risk factors already described permits the entry of lipids and inflammatory cells into the artery wall. Once in the artery, monocytes differentiate into macrophages which take up the lipid and become foam cell macrophages. This results in the formation of lesions termed “fatty streaks,” recognized as the onset of atherosclerosis Fatty streaks are small, slightly raised lesions caused by focal collections of foam cell macrophages in the intima. They may be precursors of larger atherosclerotic plaques, but may also regress. Progression of the fatty streak to a more complex lesion occurs due to the formation of a necrotic core and a fibrous cap Foam cell macrophages, engorged with lipid, begin to die and release their contents, which contributes to the formation of a necrotic core. The release of the cytoplasmic contents of the foam cells leads to the accumulation of extracellular lipids and growth factors which induce infl ammation. The occurrence of VSMC migration and proliferation results in the formation of a fi brous cap. VSMCs migrate into the intima where they proliferate and deposit extracellular matrix. Stable advanced plaque is formed due to increased number of cells and matrix. The size and composition of the plaque determine its outcome.

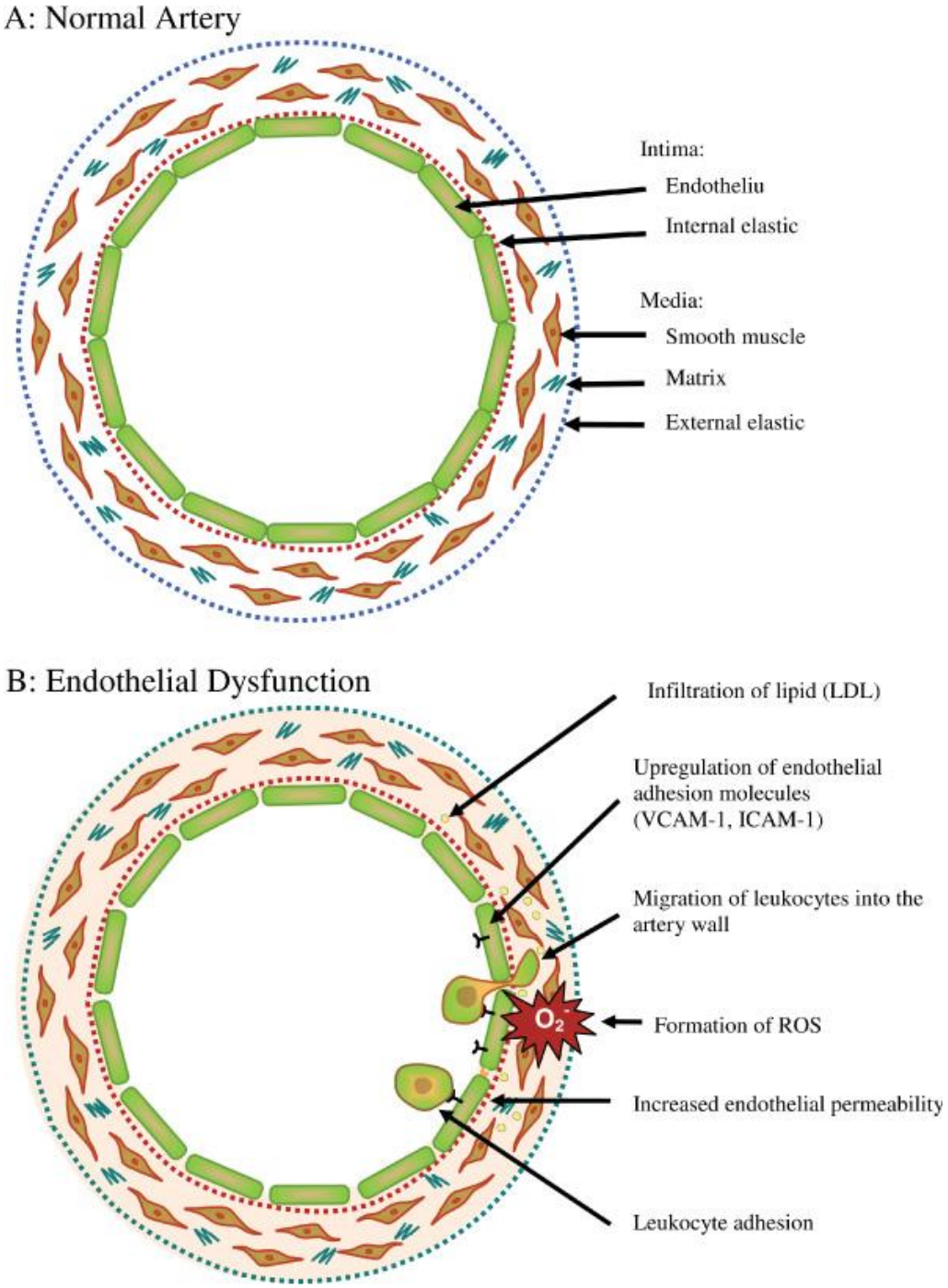
Classification schemes have been devised to categorize the various plaque types.[16-19]

1. unstable plaque

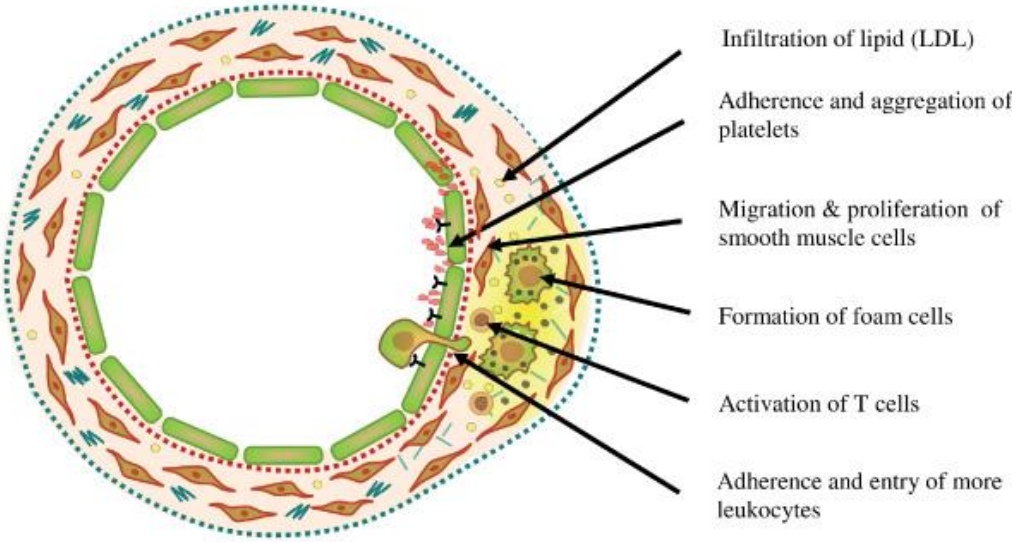
2.stable plaque

Rupture of the plaque cause thrombus formation.However, plaque rupture does not always lead to occlusion of the artery and the plaque may restabilize and heal over.[20] This is at a cost since the “ healed plaque” is larger and repeated episodes of plaque rupture and healing is associated with a greater incidence of a fatal event.[21]

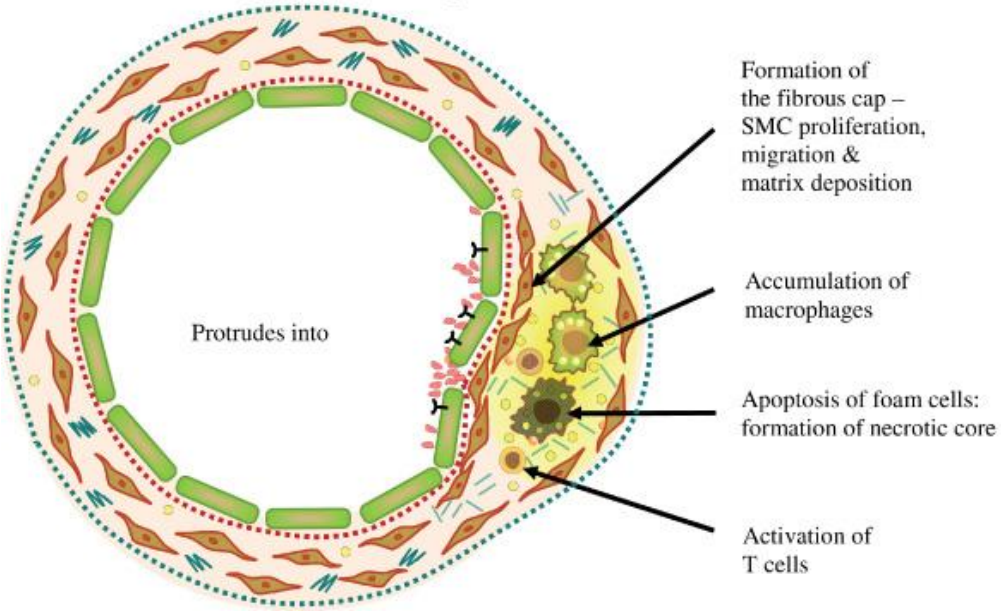
Stages of atherosclerotic plaque formation :



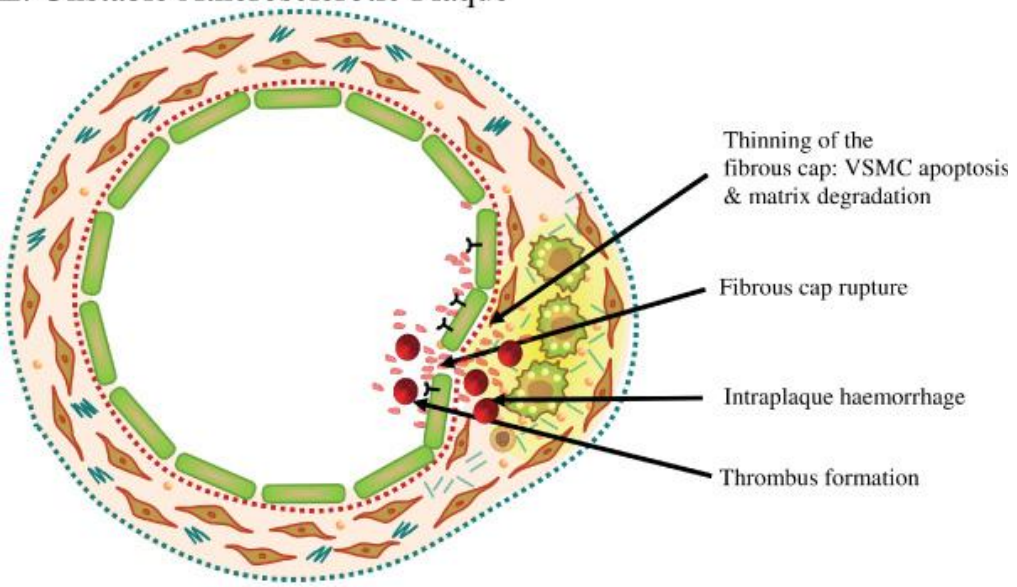
C: Fatty Streak Formation



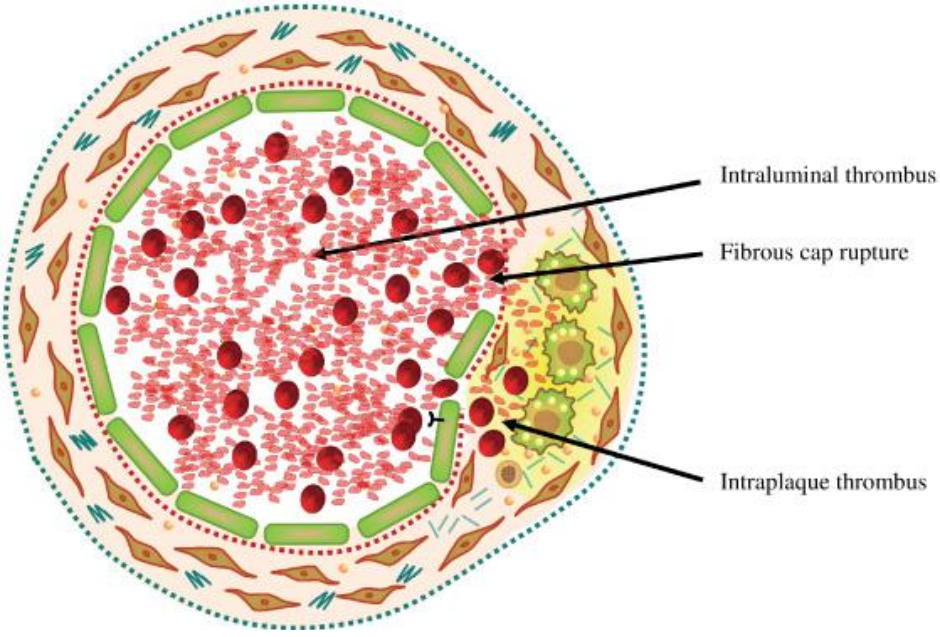
D: Stable Atherosclerotic Plaque



E: Unstable Atherosclerotic Plaque



F: Ruptured Atherosclerotic Plaque



EFFECT OF C-REACTIVE PROTEIN ON ATHEROSCLEROSIS:

Raised C-reactive protein (CRP) is a marker of systemic inflammation, which predicts cardiovascular events such as stroke and myocardial infarction among apparently healthy individuals.[13] Moreover elevated CRP levels are associated with an increase risk of recurrent infarction or death.[22] The grade of immunoreactivity of CRP ha been found to be positively correlated with the size of coronary plaques, as well as the coronary intima media wall thickness (IMT).

Recently, Zhang et al.[23] demonstrated the existence of CRP in human coronary arteries and observed a positive correlation between increased coronary IMT and the grade of CRP immunoreactivity

EPILEPSY AND VASCULAR DISEASE:

Epidemiology :

Several studies demonstrated positive correlations between epilepsy and vascular disease.Mortality ratio due to ischemic heart disease in epilepsy patients is 1.2 to 2.5.[8,24] An Mortality ratio of 10.7 reported in a chinese study on death certificates due to myocardial infarction ,[25] and myocardial ischemia was positively correlated with epilepsy.[26] 30% to 60% of epileptic patients showed significantly increased milder form of ischemic heart disease.[8,27] A Stronger

correlations between cerebrovascular disease and epilepsy was seen, with morbidity of 7 and mortality ratios of 3.7 to 5.3[24] in one study.[27]

A low prevalence of ischemic heart disease and 29% lower mortality due to heart disease who were on enzyme-inducing AEDs was seen in a Finnish study.[28] It is possible that this could be due to genetic variants in Finnish population.no significant differences in coronary risk factors was found between epileptic patients and controls in a Norwegian study.[29]

Enzyme induction effects of AEDs on cholestrol:

The enzyme-inducing AEDs carbamazepine(CBZ), phenytoin (PHT), primidone (PRM) and phenobarbital (PB), induces the cytochrome P450 system which play a role in the synthesis of cholesterol.

In the synthesis of cholesterol pathway CYP51A1 enzyme,catalyzes the reaction of convertion of lanosterol to cholesterol intermediates[30] which are further metabolished. When there is inhibition of the enzyme which metabolise these cholesterol intermediates, these intermediates increase Which in turn inhibit the rate-limiting step of cholesterol synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A reductase and slow the synthesis of cholesterol this is shown in a animal model but not studied extensively in human.[31] According to this, induction of

CYP51A enzyme increase metabolism of these cholesterol intermediates and reduced feedback inhibition.thereby increasing cholesterol synthesis. An enzyme-inducing AED such as CBZ,PHT,PB should raise serum cholesterol whereas valproic acid (VPA), an enzyme-inhibiting drug, should reduce the production of cholesterol.

Enzyme-inducing AEDs and lipid levels:

Studies have shown that the enzyme inducers CBZ, PB, PHT, and PRM can lead to increased serum cholesterol levels. Significant Elevation of total cholesterol and lowdensity lipoprotein (LDL) cholesterol were found with CBZ use in various studies.[32-40]

Very less studies are available in PHT, with some studies showing nonsignificant increase in total cholesterol along with increased high-density lipoprotein cholesterol (HDL-C).[42,43] There is only one study which shows significant elevations in total cholesterol demonstrated and low density lipoprotein (LDL) cholesterol.[44] PB also found to been associated with increased total cholesterol and LDL-C in children[45] and adults.[40] In a single study Primidone, was associated with higher total cholesterol and HDL-C as well as total cholesterol/HDL-C ratios in children with epilepsy.[46]

Thus, enzyme-inducing AEDs increase total cholesterol in many studies as would be expected by the enzyme induction hypothesis. There is a study, in which enzyme-inducing AEDs CBZ and PHT users who were switched to the non-enzyme-inducing agents lamotrigine or levetiracetam had significant decreases in total cholesterol and LDL-C levels.[44] which Support the enzyme induction hypothesis. There is another study in which patients on CBZ who were switched to oxcarbazepine a weak enzyme-inducer had decreased total serum cholesterol.[47] VPA is associated with lower serum LDL and/or total cholesterol in children and adults in many studies [34,36,37,40,43,48]

Effects of AEDs on C-reactive protein:

C-reactive protein (CRP), is an inflammatory marker and also a marker of vascular disease. The normal range for CRP is <6mg/l. Baseline CRP levelsis an independent vascular risk markers for cardiovascular disease.[49-52] CRP was elevated in patients on mixed AEDs, compared to controls.[52] There was a significant reduction of CRP, when patients on enzyme-inducing AEDs were changed to nonenzyme-inducing agents.[44] The mechanism by which enzyme-inducing AEDs increases CRP is not known.

Effects of AEDs on carotid intima-media thickness:

It is still not clear whether increase in vascular risk factors by enzyme-inducing AEDs results in increased incidence of ischemic events. Carotid intima-media thickness is a marker of atherosclerosis and its increase is significantly associated with major vascular events as established in many studies.[53-55] According to a study[56] patients treated with enzyme-inducing AEDs showed increased Carotid intima-media thickness when compared to controls. In another study patients who have taken CBZ showed increased Carotid intima-media thickness than patients on valproate, whereas patients on VPA had increased Carotid intima-media thickness than untreated epileptic patients.[57]In pediatric epileptic patients VPA increases Carotid intima-media thickness without increasing lipid profile.[58]There is positive correlation between duration of AEDs and Carotid intima-media thickness.[52]

The above studies established that enzyme-inducing AEDs is significantly associated with vascular risk factors. The mechanism by which VPA alters vascular risk factors is not still clear.

Adverse Effects of Antiepileptic Drugs:

Treatment failure occurs due to Adverse effects of antiepileptic drugs (AEDs) in upto 40% of epileptic patients . These adverse effects can have a considerable impact on quality of life.

There are five types of adverse effects of AEDs

Type A is a acute one due to pharmacological action of the drug .

Type B is a idiosyncratic reaction.

Type C is due to chronic effects.

Type D is a delayed reaction.

Type E is a drug interactions.

Carbamazepine:

- MECHANISM OF ACTION
    - Blocks voltage-activated Na channels
    - Reduces polysynaptic responses
    - Blocks post-tetanic potentiation
    - Depresses thalamic potentials
    - Depresses bulbar and polysynaptic reflexes.
- ADVERSE EFFECTS
    - Most Common Adverse Events in Clinical Trials
        - Tremor
        - Rash
        - Sedation
        - Ataxia
        - Nausea
        - Diplopia
        - Weight gain

Oxcarbazepine:

- Oxcarbazepine blocks sodium-dependent action potentials on the basis of voltage- and use-dependent limitation of action potential firing (indirect effect).
- Monohydroxy derivative (MHD) reduces glutamatergic synaptic transmission and high-voltage N-type Ca^{2+} currents

ADVERSE EFFECTS

In general, the most frequently reported side effects of oxcarbazepine include fatigue, headache, dizziness, somnolence, ataxia, nausea/vomiting, and diplopia. Other frequently reported adverse effects included nausea, rash, abnormal thinking, and acne. Oxcarbazepine and VPA were equally well tolerated in monotherapy; the adverse effects of oxcarbazepine were similar to that previously observed. Significant hyponatremia and Stevens-Johnson syndrome has been reported with oxcarbazepine.

Phenobarbital, Primidone:

- MECHANISM OF ACTION
  - Primidone metabolized to phenobarbital
  - Enhance Î³-aminobutyric acid (GABA) receptor-mediated postsynaptic chloride currents
  - Attenuates presynaptic calcium-dependent potentials.

- ADVERSE EFFECTS
    - Most Common Adverse Events in Clinical Trials
        - Sedation
        - Rash
        - Cognitive dysfunction
        - Hyperactivity
        - Ataxia
    - Idiosyncratic reactions.
- **Phenytoin**
- MECHANISM OF ACTION
    - Blocks voltage-activated Na channels
- ADVERSE EFFECTS
    - The Five Most Common Adverse Events in Clinical Trials. Nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion
    - Differences in Adverse Effects Profiles in Non‟Epilepsy Trials versus Epilepsy Trials. None systematically studied
    - Idiosyncratic
        - Others
            - Gingival hyperplasia
            - Lymphadenopathy

        - Sensory peripheral neuropathy
        - Osteomalacia

- **Topiramate**
- MECHANISM OF ACTION
    - Blocks voltage-activated Na channels
    - Blocks AMPA/kainate type of glutamate receptor
    - Enhances Î³-aminobutyric acid (GABA)“mediated chloride flux
    - Reduces amplitude of high-amplitude calcium currents
    - Activates potassium conductance
    - Carbonic anhydrase inhibitor
- ADVERSE EFFECTS
    - Five Most Common Adverse Events in Clinical Trials
        - At 200- to 400-mg/day dosage as adjunctive therapy, the five most common adverse effects were somnolence, dizziness, ataxia, nervousness, and fatigue.

Valproic Acid

- MECHANISM OF ACTION
    - Blocks voltage-activated Na channels
    - Activates calcium dependant potassium conductance

- ADVERSE EFFECTS
    - The five most common adverse effects in clinical trials
        - Nausea, somnolence, tremor, dizziness, asthenia
    - The three most common adverse effects that caused discontinuations in clinical trials (epilepsy)
        - Not stated
    - Differences in adverse effect profiles in non‘‘epilepsy trials versus epilepsy trials
        - Tremor was less likely to be reported in mania and headache trials than in epilepsy trials.
    - Idiosyncratic
        - Rash Rate. 6% rate in clinical trials
        - Serious Rash Rate. Not noted
        - Hepatic Dysfunction Rate. Rate not stated, but cases of serious hepatic dysfunction have been reported, most within first 6 months of therapy. The highest risk groups for hepatic failure are children younger than 2 years, those receiving multiple AEDs, or those with congenital metabolic disorders.
        - Renal Stones. Not noted

        - Hematologic Dysfunction Rate. Thrombocytopenia in up to 27%
        - Pancreatitis. Rate 0.8% in clinical trials; may be rapid and fatal
        - Hyperammonemia. More likely to be asymptomatic

Zonisamide

- MECHANISM OF ACTION
    - Blocks repetitive firing of voltage-sensitive sodium channels
    - Reduces voltage-sensitive T-type (transient inward) calcium channels; it does not affect the L-type calcium channels
    - Has weak activity in inhibiting carbonic anhydrase
- ADVERSE EFFECTS
    - Tolerability was formally assessed in three major add-on trials. The most frequently reported adverse events (10% of patients) were fatigue, dizziness, somnolence, anorexia, abnormal thinking, and ataxia Idiosyncratic.

MATERIALS & METHODS

SETTINGS: Patients attending epilepsy clinic in neurology department, Madras Medical College and Rajiv Gandhi Government general hospital Chennai - 600 003.

ETHICAL APPROVAL:

Obtained

STUDY DESIGN:

A cross sectional study design was chosen.

PERIOD OF STUDY:

JAN 2012 to DEC 2012

SAMPLE SIZE

Cases: 100, Controls: 100 .

INCLUSION CRITERIA:

All epilepsy patient receiving AED monotherapy for more than 2 years.

Hundred healthy volunteers included as control.

EXCLUSION CRITERIA:

Patients with Epilepsy with the following conditions were excluded from the study

1.Patients who discontinued AED for more than 2 weeks.

2.Malabsorption syndrome

3.Nephrotic syndrome

4.Diabetes mellitus

5.Thyroid disorders

6.Liver disorders

7.Intake drugs like

a. Diuretics

b. Oral contraceptives

8.Lipid storage disorders

STUDY POPULATION:

Hundred epileptic patients and age and sex matched healthy controls were selected for the study from epilepsy clinic and outpatient department of Rajiv Government General hospital Chennai, after

thorough history taking and clinical examination and by exclusion criteria.

LABAROTARY MEASUREMENTS

After ensuring 12 hours overnight fasting, normal diet (without any fat restriction) for previous two weeks, and abstinence from alcohol, the blood samples were collected from Epilepsy patients & healthy controls. From the blood, serum was separated & stored in refrigerator. Then this was used for lipoprotein and CRP analytical studies.

Concentration of total cholesterol, HDL-cholesterol, and triglycerides were assessed enzymatically with commercially available reagents. Concentration of LDL- cholesterol was calculated by use of the Friedewald equation for participants who had triglycerides (< 400 mg/dl)

$$LDL = TC - HDL\text{-}c - TGL/5.$$

Common carotid artery IMT was measured by B-mode ultrasound System to assess the extent of atherosclerosis . We scanned both the left and right Common carotid artery, defined as the 1-cm vascular wall segment of the carotid artery immediately proximal to the dilation of the bifurcation plane An optimal longitudinal image was saved and the IMT was analyzed using a computerized image analysis system.

The vascular risk marker CRP was measured by latex agglutination method. The CRP was determined using a Dimension® RxL clinical chemistry analyzer in a serum specimen with CRP FlexTM reagent cartridges. A concentration more than 6 mg/L was defined as elevated according to the reference values of our laboratory.

FINANCIAL SUPPORT: nil.

CONFLICT OF INTEREST: nil

STATISTICAL ANALYSIS

Statistical analysis was carried out for 200 participants [100 epilespy patients, 100 controls] after categorizing each variable. Base line data was collected from patients Age, sex, AED, dosage duration of AED, carotid intima media thickness, Lipid profile, BMI, CRP were analyzed.

The significance of difference in means between two groups were analyzed by student t-test. The correlation between duration of AED and average carotid intima media thickness was calculated by using the Pearson's correlation coefficient method.

Statistical significance was taken when p value was < 0.05. Statistical analysis was carried out using standard formulae. Microsoft excel 2007 and SPSS (statistical package for social sciences) version 20 software was used for data entry and analysis.

RESULTS AND OBSERVATION

In our study , 100 epileptic patients matched with 100 healthy controls were studied for cardiovascular risk factors namely lipid profile (TC, LDL, HDL,TGL), body mass index (BMI), C-reactive protein (CRP) and carotid intima media thickness (CIMT) and the following observation were made. Patients with age group ranging from 10 to 90 years were studied.

Table : 1 - AGE DISTRIBUTION IN CONTROL AND STUDY GROUP

AGE IN YEARS	CONTROL	STUDY
10 -20	22	22
21 -30	39	35
31 -40	21	21
41 -50	08	09
51 -60	08	10
61 -70	01	02
71 -80	01	0
81 -90	0	01

In the control group 22 were in the 10-20 age group,39 were in the 21-30 age group, 21 were in the 31-40 age group,8 were in the 41-50,51-60 age groups and 1 were in the 61-70, 71-80 age groups.

In the study group 22 were in the 10-20 age group,35 were in the 21-30 age group, 21 were in the 31-40 age group,9 were in the 41-50, age group, 10 were in the 51-60 age group,2 were in the 61-70 age group and

1 were in the 81-90 age groups. More epileptic patients were in the age group of 21 to 30 years.

TABLE : 2 - AGE DISTRIBUTION IN CONTROL AND STUDY GROUP

	Group	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Control	100	30.65	13.497	1.350
	Study	100	31.68	14.466	1.447

The mean age in years in control group were 30.65 and in study group were 31.68.

TABLE:3 - COMPARISION OF MEAN-AGE OF STUDY AND CONTROL GROUP

	t-TEST VALUE	df	P VALUE	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
Age in years	-.521	198	.603	-1.03	1.978	-4.932	2.872

Age distribution between control and AED study group is not statistically different.

TABLE:4 SEX DISTRIBUTION IN CONTROL AND STUDY GROUP

SEX	Group	
	Control	**Study**
Number of males	45	47
% of male	45%	47%
Number of female	55	53
% of female	55%	53%

In the control group 45 (45%) were male and 55 (55%) were female. In the study group 47 (47%) were male and 53 (53%) were female.

Chi Square Tests for sex between control and study

	Value	**df**	**Asymp. Sig. (2-sided) p value**
Pearson Chi-Square	.081(b)	1	.777

This study shows females preponderance of patients compared to males. But there is no significant difference in sex between control and epileptic groups.

TABLE 5: DURATION AND DOSAGE OF AEDs IN STUDY GROUP

Antiepileptic drug	No. of patients	Mean duration of AEDs(Years) with SD	Dosage Range in mg/day
PHENYTOIN	32	5.09 ±3.59	200-400
CARBAMAZEPINE	28	8.35 ±4.49	400-1200
VALPROATE	21	6.43±3.21	400-1600
PHENOBARBITONE	19	8.37 ±4.03	15-60

The mean duration of AED therapy in carbamazepine and phenobarbitone were higher than valproate and phenytoin groups.

FIGURE 1: SEX DISTRIBUTION IN CONTROL AND STUDY GROUP

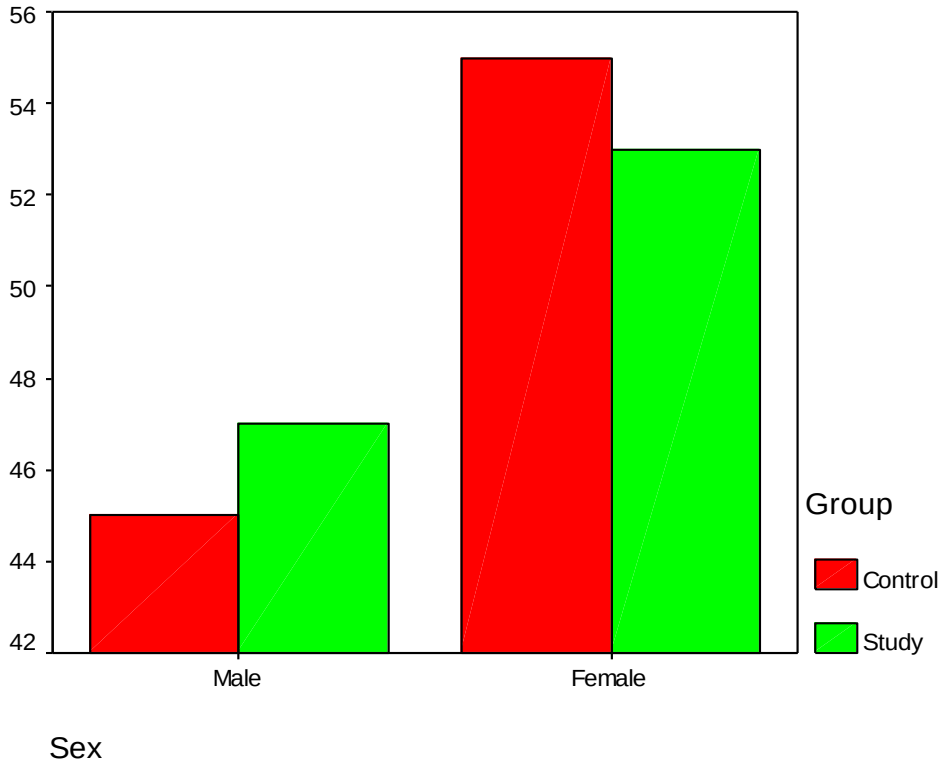


FIGURE 2: AGE DISTRIBUTION IN CONTROL AND STUDY GROUP

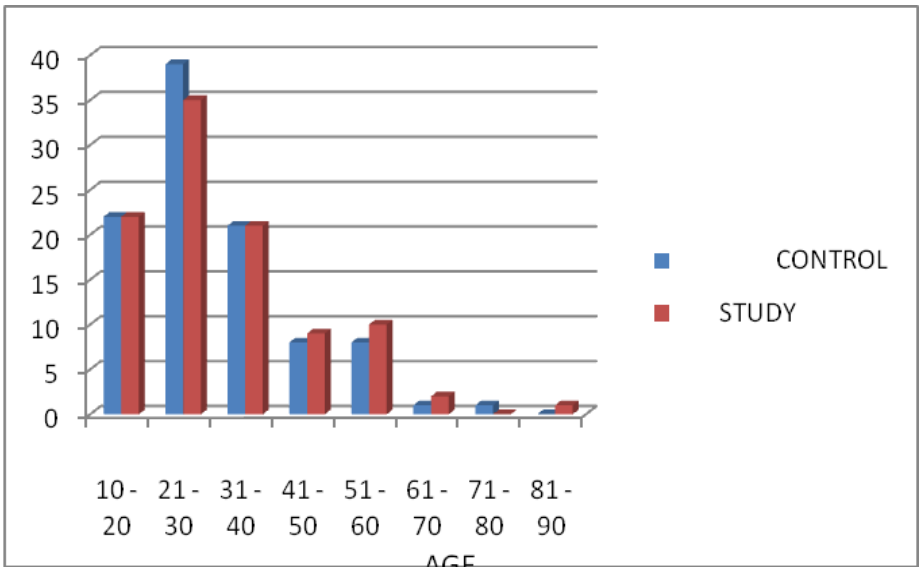


FIGURE 3:COMPARISION OF CRP BETWEEN CONTROL AND AED GROUP

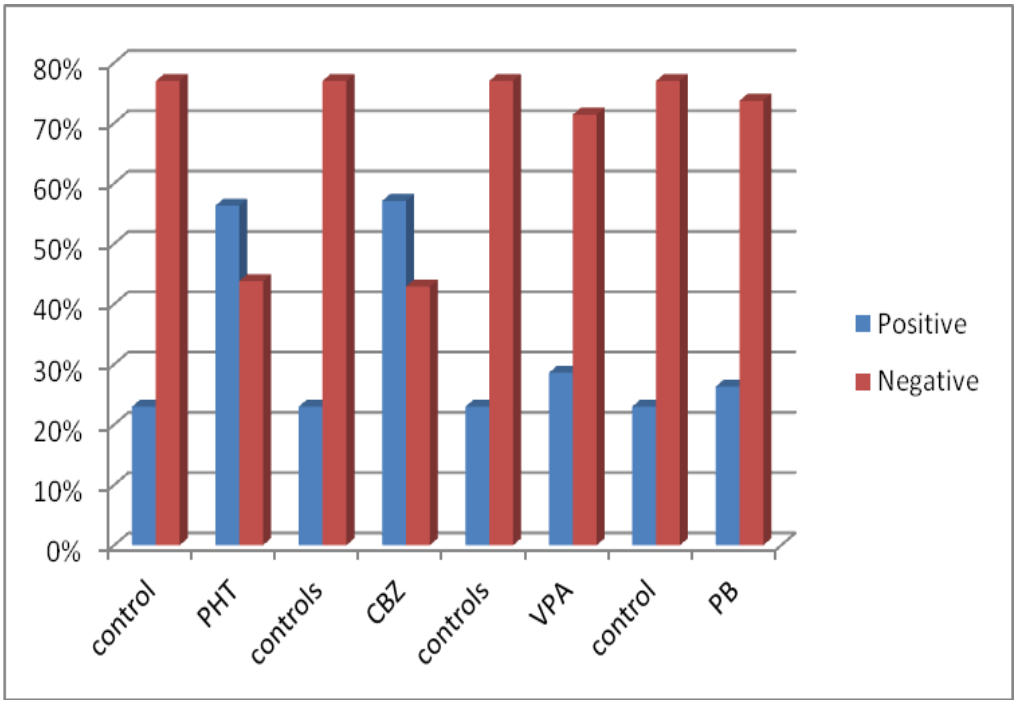
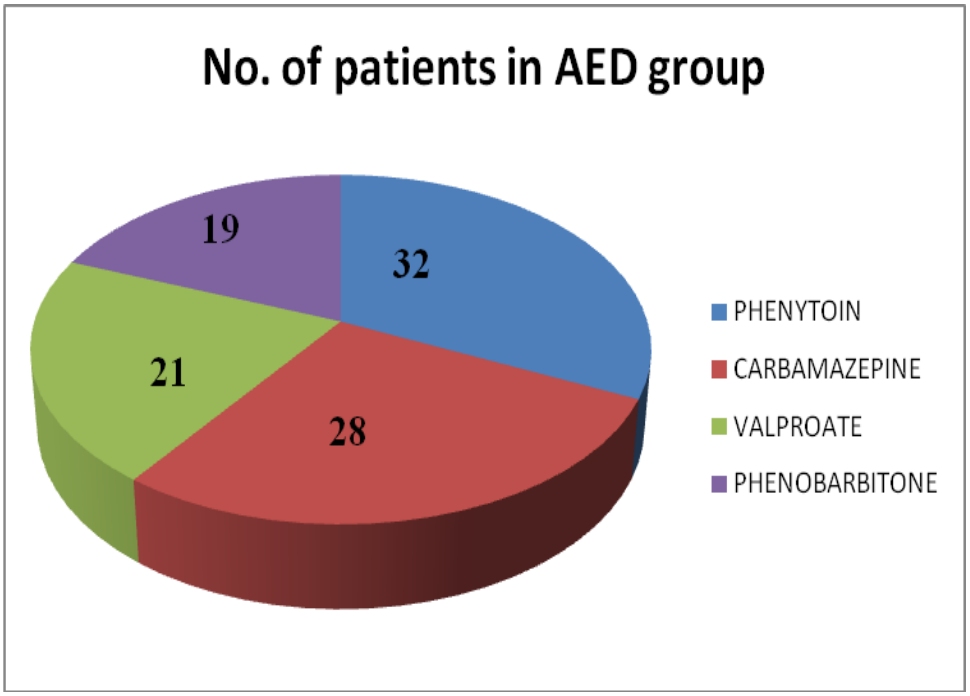


FIGURE:4 NUMBER OF PATIENTS IN AEDs GROUP.



EFFECT OF PHENYTOIN ON ATHEROSCLEROSIS RISK FACTORS:

TABLE: 6 COMPARISION OFMEAN BMI VALUES OF CONTROL AND PHENYTOIN GROUP

	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed) p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	-5.852	.000
	Phenytoin	32	26.241	3.7119	.6562	-4.936	.000

Table: 7 COMPARISION OF MEAN LIPID LEVELS OF CONTROL AND PHENYTOIN GROUP

Lipids in mgs%	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed) p value
TC	Control	100	158.77	9.700	.970	.721	.472
	Phenytoin	32	157.47	5.542	.980	.944	.348
LDL	Control	100	95.88	9.213	.921	-.465	.642
	Phenytoin	32	96.69	5.905	1.044	-.580	.563
HDL	Control	100	32.38	3.966	.397	-1.801	.074
	Phenytoin	32	33.75	2.929	.518	-2.100	.039
TGL	Control	100	148.69	17.904	1.790	.148	.883
	Phenytoin	32	148.16	17.428	3.081	.150	.881

TABLE: 8 COMPARISION OF MEANS-IMT VALUES OF CONTROL AND PHENYTOIN GROUP

CCA-IMT (mm)	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed) p value
IMT-Right	Control	100	.6175	.07120	.00712	-6.548	.000
	Phenytoin	32	.7544	.16800	.02970	-4.482	.000
IMT- Left	Control	100	.6254	.07656	.00766	-6.785	.000
	Phenytoin	32	.7409	.10375	.01834	-5.813	.000
IMT – Average	Control	100	.6215	.05114	.00511	-9.550	.000
	Phenytoin	32	.7477	.09696	.01714	-7.056	.000

This study shows epileptic patients on phenytoin has significantly raised BMI and Average IMT mean values when compared to Controls.

Table: 9 COMPARISION OF MEANS BMI VALUES OF CONTROL AND CARBAMZEPINE GROUP

	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed) p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	-.993	.323
	Carbamzepine	28	23.289	2.1605	.4083	-1.114	.270

Table: 10 COMPARISION OF MEANS LIPID LEVELS OF CONTROL AND CARBAMZEPINE GROUP

Lipids in mgs%	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed) p value
TC	Control	100	158.77	9.700	.970	-6.128	.000
	Carbamzepine	28	173.93	16.720	3.160	-4.586	.000
LDL	Control	100	95.88	9.213	.921	-4.981	.000
	Carbamzepine	28	107.68	16.171	3.056	-3.697	.001
HDL	Control	100	32.38	3.966	.397	.226	.822
	Carbamzepine	28	32.18	4.839	.914	.202	.841
TGL	Control	100	148.69	17.904	1.790	-1.509	.134
	Carbamzepine	28	154.07	11.062	2.090	-1.955	.055

TABLE: 11 COMPARISION OF MEANS IMT VALUES OF CONTROL AND CARBAMZEPINE GROUP

CCA- IMT (mm)	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-3.993	.000
	Carbamzepine	28	.6914	.12808	.02421	-2.930	.006
IMT- Left	Control	100	.6254	.07656	.00766	-4.955	.000
	Carbamzepine	28	.7196	.12426	.02348	-3.816	.001
IMT - Average	Control	100	.6215	.05114	.00511	-6.376	.000
	Carbamzepine	28	.7055	.09035	.01708	-4.717	.000

This study shows epileptic patients on carbamazepine has significantly raised TC, LDL-C and Average IMT mean values when compared to Controls .

TABLE: 12 COMPARISION OF MEANS BMI VALUES OF CONTROL AND VALPROATE GROUP

	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	-2.006	.047
	Sodium Valproate	21	24.095	3.4379	.7502	-1.694	.103

TABLE: 13 COMPARISION OF MEANS LIPID LEVELS OF CONTROL AND VALPROATE GROUP

Lipids in mgs%	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
TC	Control	100	158.77	9.700	.970	-.018	.986
	Sodium Valproate	21	158.81	5.980	1.305	-.024	.981
LDL	Control	100	95.88	9.213	.921	-1.185	.238
	Sodium Valproate	21	98.38	6.305	1.376	-1.510	.139
HDL	Control	100	32.38	3.966	.397	-1.758	.081
	Sodium Valproate	21	34.00	3.130	.683	-2.051	.048
TGL	Control	100	148.69	17.904	1.790	-1.302	.195
	Sodium Valproate	21	154.05	12.690	2.769	-1.625	.112

TABLE: 14 COMPARISION OF MEAN IMT VALUES OF CONTROL AND VALPROATE GROUP

CCA- IMT (mm)	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-5.203	.000
	Sodium Valproate	21	.7157	.10815	.02360	-3.984	.001
IMT- Left	Control	100	.6254	.07656	.00766	-3.618	.000
	Sodium Valproate	21	.6924	.07987	.01743	-3.519	.001
IMT - Average	Control	100	.6215	.05114	.00511	-6.248	.000
	Sodium Valproate	21	.7040	.07143	.01559	-5.035	.000

This study shows epileptic on sodium valproate has significantly raised BMI and Average IMT mean values when compared to Controls.

Table: 15 COMPARISION OF MEANS BMI VALUES OF CONTROL AND PHENOBARBITONE GROUP

	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
BMI kg/m^2	Control	100	22.747	2.6520	.2652	1.695	.093
	Phenobarbitone	19	21.642	2.3253	.5335	1.855	.074

TABLE: 16 COMPARISION OF MEAN LIPID LEVES OF CONTROL AND PHENOBARBITONE GROUP

Lipids in mgs%	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
TC	Control	100	158.77	9.700	.970	-5.523	.000
	Phenobarbitone	19	174.11	16.806	3.856	-3.857	.001
LDL	Control	100	95.88	9.213	.921	-4.212	.000
	Phenobarbitone	19	107.89	19.430	4.458	-2.640	.016
HDL	Control	100	32.38	3.966	.397	-.821	.413
	Phenobarbitone	19	33.26	5.801	1.331	-.636	.532
TGL	Control	100	148.69	17.904	1.790	-.573	.567
	Phenobarbitone	19	151.16	12.619	2.895	-.725	.473
	Phenobarbitone	19	.7126	.11035	.02531	-3.618	.002

This study shows epileptic patients on Phenobarbitone has significantly raised TC and LDL-C mean values when compared to Controls.

TABLE: 17 COMPARISION OF MEAN IMT VALUES OF CONTROL AND PHENOBARBITONE GROUP

CCA- IMT (mm)	Sub Group	N	Mean	Std. Deviation	Std. Error Mean	t	Sig. (2-tailed)p value
IMT- Right	Control	100	.6175	.07120	.00712	-4.842	.000
	Phenobarbitone	19	.7126	.11035	.02531	-3.618	.002
IMT- Left	Control	100	.6254	.07656	.00766	-2.154	.033
	Phenobarbitone	19	.6674	.08458	.01940	-2.012	.056
IMT - Average	Control	100	.6215	.05114	.00511	-4.802	.000
	Phenobarbitone	19	.6900	.08223	.01886	-3.507	.002

This shows patients on Phenobarbitone has significantly raised Average IMT mean values when compared to Controls

TABLE: 18 CRP. LEVEL – AN ANALYSIS BETWEEN CONTROL AND AED GROUP

CRP mg/l	PHENYTOIN		CARBAMAZEPINE		VALPROATE		PHENOBARBITONE	
	control	study	controls	study	controls	study	control	study
Positive >6mg/l	23	18	23	16	23	6	23	5
Negative <6 mg/l	77	14	77	12	77	15	77	14
Positive % within subgroup	23%	56.3%	23%	57.1%	23%	28.6%	23%	26.3%
Negative % within subgroup	77%	43.8%	77%	42.9%	77%	71.4%	77%	73.7%

TABLE:19 COMPARISION OF CRP BETWEEN CONTROL AND AED GROUP

	Pearson Chi-Square Value	**df**	**Asymp. Sig. (2-sided) P value**
PHENYTOIN	12.516(b)	1	.000
CARBAMAZEPINE	12.037(b)	1	.001
VALPROATE	.296(b)	1	.587
PHENOBARBITONE	.098(b	1	.755

CRP significantly positive in phenytoin and carbamazepine groups when compared to controls.

Table:20 CORRELATION BETWEEN DURATION OF AED AND AVERAGE-IMT.

	PHENYTOIN	**CARBAMAZEPINE**	**VALPROATE**	**PHENOBARBITONE**
PEARSON CORRELATION	.446	.115	.405	.597
P value	.011	.56	.068	.007

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

By pearson correlation,Phenytoin and phenobarbitone shows significant positive correlation between duration of AED and Average IMT.

After adjusting for age and sex by regression analysis,effect of phenytoin on average CCA-IMT does not show significant difference where as duration of phenobarbitone therapy has a significant effect on CCA-IMT.

TABLE : 21 SUMMARY OF OBSERVATIONS:

risk factors	**phenytoin**	**carbamazepine**	**valproate**	**phenobarbitone**
BMI	**↑(S)**	NS	**↑(S)**	NS
TC	NS	**↑(S)**	NS	**↑(S)**
LDL-C	NS	**↑(S)**	NS	**↑(S)**
HDL-C	NS	NS	NS	NS
TGL	NS	NS	NS	NS
CCA-IMT	**↑(S)**	**↑(S)**	**↑(S)**	**↑(S)**
CRP	**↑(S)**	**↑(S)**	↑NS	↑NS
Correlation between duration of AEDs and average CCA-IMT	Insignificant Positive correlation	Insignificant Positive correlation	Insignificant Positive correlation	Significant Positive correlation

S – Significant

NS – Not Significant

↑ - Increased

DISCUSSION

Patients with epilepsy have to undergo chronic treatment with antiepileptic drugs. Most of these individuals undertake treatment during most productive period of their lifetime. It is not only important that their epileptic seizures have to be under control but also adverse effects due to long term antiepileptic drugs (AED) intake have to be minimal.

In this context there have been few studies that have indicated that long term AED intake has been associated with increased vascular risk factors. A Finnish[28] study had shown to the contrary that the mortality due to cardiovascular risk in patients taking long term AEDs was significantly lower. Another Norwegian study[29] has shown that the risk for coronary events in patient with epilepsy versus controls was not significantly different.

In this background , in our setting a large majority of our patients are in the most productive life taking long term AEDs. As our hospital provides only old generation AEDs, we found that it is informative to study the long term effect of old generation AED's, on cardiovascular risk factors especially as they are in the most productive age of their lives. With this consideration we analysed patients taking AED monotherapy more than two years with age and sex matched controls. We analysed

effect of AED on primary cardiovascular (BMI), C-reactive protein(CRP) and carotid intima media thickness (CIMT). risk factors namely lipid profile (TC, LDL, HDL,TGL), body mass index

In this analysis we found that patients taking monotherapy with phenobarbitone (PB) and carbamazepine (CBZ) had significantly increased total cholesterol, low density lipoprotein cholesterol and common carotid artery intima media thickness (CCA-IMT) in comparison to age and sex matched controls. In previous studies [26-31] Bramswig etal[59] has shown similar results in that total cholesterol, low density lipoprotein and intima media thickness significantly correlated to carbamazepine intake. Also similar studies by Mintzer et al[44]., 2009; Belcastro et al[60]., 2010; Svalheim et al[61].,2010, have shown that carbamazepine is significantly associated with increased total cholesterol and atherogenic (Non HDL) cholesterol. This effect of carbamazepine may be due to enzyme inducing effects of the drug. The reason for which have been detailed earlier.

Very few studies are available regarding phenytoin intake and lipid levels. some studies showing nonsignificant elevations in total cholesterol and high-density lipoprotein cholesterol (HDL-C)[42,43] Long term phenytoin intake which was significantly associated with increased total cholesterol, LDL-C levels in Mintzer et al[44], was not significant in our

study. With patients on chronic intake of phenytoin in our study though the levels of LDL-C was elevated the difference in elevation was not statistically significant.

The reason for the same could be due to lower average dose prescribed in our patients compared to previous studies in western population.

As our's is a developing country compared to western country, a significantly large number of patients are on phenobarbitone monotherapy. We found in this group the levels of total cholesterol, LDL-C are significantly elevated which is in comparison to previous western data.[33-37,45]This effect of phenobarbitone could be explained due to its enzyme inducing effects. This finding is of great importance as phenobarbitone is slowly regaining its importance in patients with epilepsy in developing countries as a monotherapy, primarily due to its cost factors.[62]

Chronic valproate intake is not associated with significant elevation in total cholesterol, low density lipoprotein and triglyceride in children and adults.[34,36,37,43] The studies citated earlier have hypothesized based on animal models, that non ezyme inducing effect of valproate could be the reason for the same. In our also we found that valproate

intake was not significantly associated with total cholesterol, low density lipoprotein cholesterol elevations.

All the drugs in this study was associated with significant increase in common carotid artery intima media thickness (CCA-IMT) similar to Schwaninger et al.[56] The reason could be due to increase in lipid levels in enzyme inducing drugs.

However in valproate the same could not be explained as lipid levels were not significantly elevated. Previous studies have also shown similar results.

Chuang HY et al.[63] have shown positive correlation of vascular risk factors with duration of AED in the CBZ,PH and VPA treatment groups but in our study, in patients who was on Valproate , phenytoin and carbamazepine the duration of therapy was not significantly associated with increased common carotid artery intima media thickness (CCA IMT). The reason for this could be due to different mechanism of action of each drug. In the case of valproate as discussed earlier there was no significant elevation in total cholesterol, low density lipoprotein which could be the cause for no significant increase in common carotid artery intima media thickness (CCA-IMT) The reason that, phenytoin and carbamazepine duration of therapy not contributing to common carotid

artery intima media thickness (CCA-IMT), could be due to lower doses of drugs probably given in our population.

CRP has been found to be an independent risk factor for vascular disease.[49-51] However whether CRP is a direct cause for the process or whether it is an surrogate marker for the other pathological process is not clear. The role of AEDs in relation to CRP level is not well established . An article by Mintzer et al[44] has found that the level of CRP was reduced when patients were changed from enzyme inducing to non enzyme inducing agents.

In our study also we found out that patient on carbamazepine and phenytoin had significantly elevated levels of CRP. While patients on Valproate did not have significantly elevated levels of CRP. However Phenobarbitone which is an enzyme inducer did not affect levels of CRP. Though these observations correlate with studies[52] done earlier the reason for CRP levels not being elevated in patients on Phenobarbitone therapy is not clear.

Long term intake with Valproate therapy has been associated with increased body mass index which is one of the criteria for metabolic syndrome.Metabolic syndrome is an independent risk factor for cardiovascular disease. Carbamazepine has also been found to marginally increase body mass index.[66]In our study we found the Valproate and

Phenytoin were associated with increased body mass index. While Carbamazepine and Phenobarbitone therapy did not affect the same. Though Valproate effect on body mass index is well established the role of other AEDs on body mass index is not well known. Perhaps we need a large sample size to study the effect of AED monotherapy on BMI.The limitation of this study is that the quantification of CRP using various dilutions was not done. The sample size was likely to be insufficient and hence a type II error in these results cannot be ruled out.

From the above observation it is clear that AEDs have a variably effect on each of the vascular risk factors, probably due to different mechanism. This effect has to be studied on a larger sample size to assess the long term effect of anti epileptic drugs on vascular risk factors especially in those requiring long term AEDs and in elderly patients.

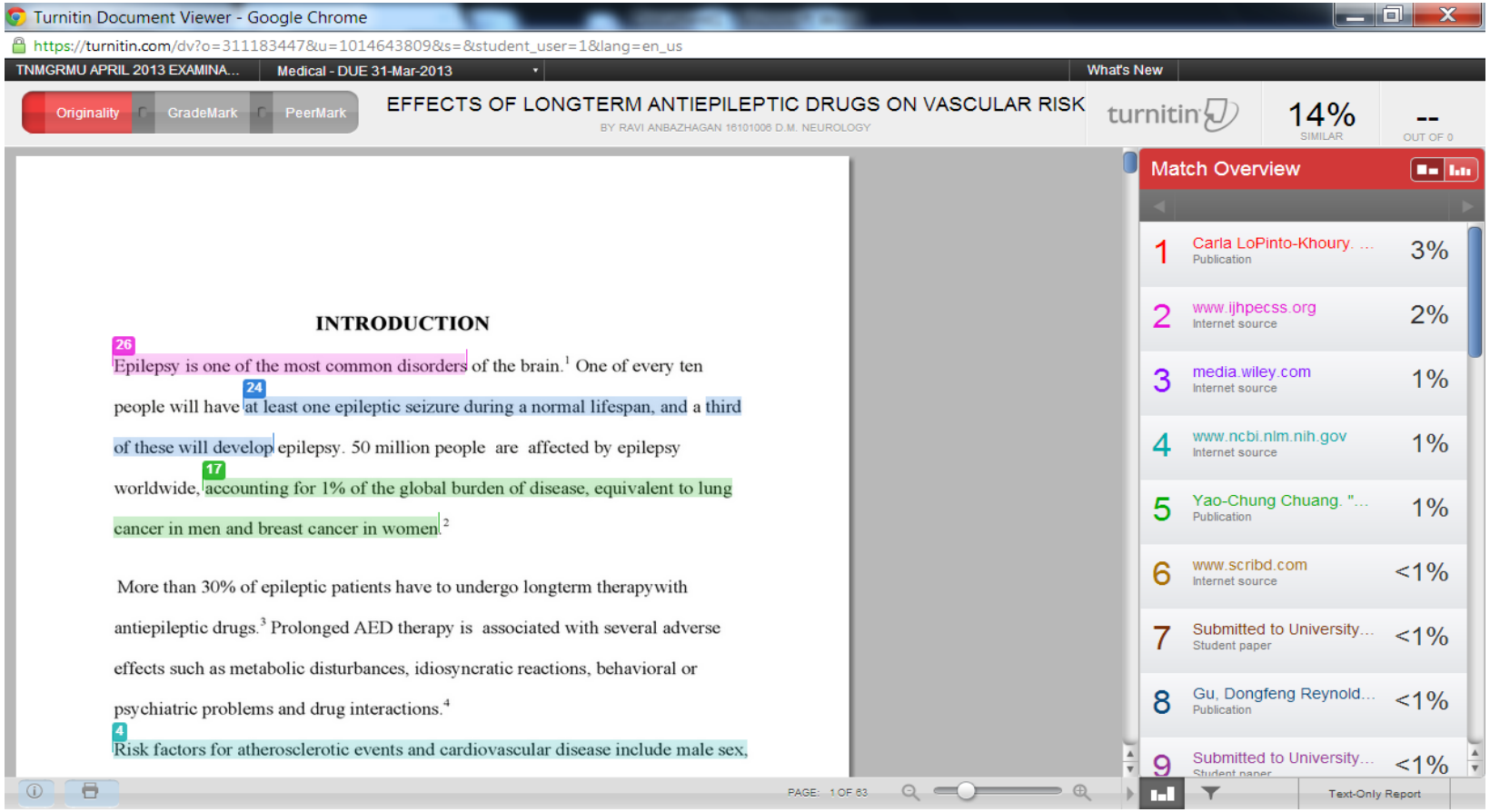
CONCLUSION

The following conclusions were observed from our study.

1. Epileptic patients on carbamazepine and phenobarbitone had significantly elevated levels of serum total cholesterol, LDL-cholesterol and CRP. HDL-cholesterol level, Triglyceride and body mass index were not significantly altered in these groups.
2. Patients on phenytoin and sodium valproate had significantly elevated body mass index. There was no significant effect on lipid levels and CRP in this group.
3. All the antiepileptic drugs in this study significantly increased the common carotid artery intima media thickness.
4. It is observed that there is significant positive correlation between duration of phenobarbitone therapy and average common carotid artery intima media thickness which was not noted with carbamazepine, phenytoin and sodium valproate.

This study of antiepileptic drugs on vascular risk factors will have a bearing on the selection of AEDs in refractory epileptic patients and elderly patients. Hence a lonterm study has to be conducted in a large sample of epileptic patients to assess the effects of AEDs on vascular risk factors especially in those requiring long term AEDs and in elderly patients.

TURNITIN-PLAGIARISM SCREEN SHOT



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Submission time	24-Mar-2013 04:11PM
Total words	8253

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INTRODUCTION Epilepsy is one of the most common disorders of the brain.1 One of every ten people will have at least one epileptic seizure during a normal lifespan, and a third of these will develop epilepsy. 50 million people are affected by epilepsy worldwide, accounting for 1% of the global burden of disease, equivalent to lung cancer in men and breast cancer in women.2 More than 30% of epileptic patients have to undergo longterm therapywith antiepileptic drugs.3 Prolonged AED therapy is associated with several adverse effects such as metabolic disturbances, idiosyncratic reactions, behavioral or psychiatric problems and drug interactions.4 Risk factors for atherosclerotic events and...

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PROFORMA

EFFECTS OF LONGTERM ANTIEPILEPTIC DRUGS ON VASCULAR RISK FACTORS AND ATHEROSCLEROSIS

PATIENT INFORMATION:

SERIAL NO.

NAME: AGE ……. YEARS

GENDER: MALE/FEMALE MIN NO.

OP NO:

HEIGHT: cm WEIGHT: kg BMI-

ADDRESS: PHONE NO

Age of onset of epilepsy:

Duration of epilepsy:

Duration of AED:

Dosage of AED in mg/day

Average seizure frequency per month during previous 1 year;

HISTORY & PRESENTATION:

SEIZURE:

Description of ictus;

Post ictal state

TYPE OF SEIZURE:

1.Primary generalized(GTCS)

2.Focal with secondary generalization

3.complex partial

4.Absence

5.Myoclonic jerks

6.others

Average no. of seizure ……..over……..(day/week/month/year)

Idiopathic / Cryptogenic

Symptomatic :

Cluster attacks

Status epilepticus

Fever /Headache/Vomiting/

Limb Weakness

Sensory disturbance

Altered behavior

Trauma

Others:

PAST HISTORY:

Type of seizure-GTCS/simple/complex/absence/Myoclonus

Frequency……per…….

Number of years in remission(before current presentation)……yrs

Type of AED used in past –

1.PHT 2.PB 3.CBZ 4.Valproate 5.oxycarbamazepine 6.Others

Febrile seizure in childhood

Simple febrile/ Complex febrile seizure

ASSOCIATED CONDITIONS:

TIA/ CVA

Head injury

Surgery

Meningoencephalitis

Congnitive decline

COMORBIDITIES

DM / Hypertension / CAD /Stroke / Hyperlipidemia /Liver disease / Kidney disease

Rheumatological illness

Medications for systemic illnesses(with duration)

PERSONAL HISTORY

Alcoholism /smoking /tobacco chewing /

Diet Vegetarian / Non vegetarian

FAMILY HISTORY

Seizure /DM /HT / CAD /Hyperlipidemia

Others

EXAMINATION:

Temperature Pulse BP mmHg pallor

Icterus Lymphadenopathy Clubbing Pedal oedema

Carotid bruit Peripheral pulsation

Thyroid swelling

Neurocutaneous markers

CVS:

RS: ABDOMEN:

CENTRAL NERVOUS SYSTEM:

Sensorium:GCS : E V M

Meningeal signs:

HMF;

Cranial nerves:

Spino motor system:

CEREBELLAR Signs

Sensory:

0thers

LAB INVESTIGATIONS

Hb % gm%

TC

DC

ESR

Blood sugar

Blood urea

Serum creatinine

Electrolytes:

X ray CHEST

USG ABDOMEN

THYROID PROFILE:

CSF:

ECG

ECHO

EEG-

FASTING LIPID PROFILE

Total Cholesterol

LDL- C

HDL- C

Triglycerides

CRP:

CT BRAIN:

MRI BRAIN:

COMMON CAROTID INTIMA MEDIA THICKNESS(CCA-IMT)

RIGHT CCA IMT –

LEFT CCA IMT –

AVERAGE CCA IMT -

AEDs DETAILS:

DIAGNOSIS:

ABBREVIATIONS

AED	-	Antiepileptic drug
BMI	–	Body mass index
CBZ	-	Carbamazepine
CCA	–	Common carotid artery
CVD	-	Cardiovascular disease
CSWSS	-	Continuous spike and wave in slow wave sleep
CHD	-	Coronary heart disease
CNS	-	Central nervous system
CIMT	-	Carotid intima media wall thickness
CRP	-	C-reactive protein
EEG	-	Electroencephalography
GTCS	–	Generalised tonic clonic seizure
HDL- C	-	High-density lipoprotein cholesterol
LDL-C	-	Low-density lipoprotein cholesterol
MI	–	Myocardial infarction
PB	-	Phenobarbitone
PHT	-	Phenytoin
PRM	-	Primidone
ROS	-	Reactive oxygen species
TC	-	Total cholesterol
TGL	-	Triglyceride
VPA	-	Valproic acid
VSMCs	-	Vascular smooth muscle cells
WHO	-	World Health Organization

S.NO.	NAME	AGE	SEX	BMI kg/m2	TC mg%	LDL mg%	HDL mg%	TGL mg%	CRP mg/L	IMT®mm	IMT(L)mm
1	Ranjith	M	39	19.4	162	104	30	139	NEGATIVE	0.54	0.52
2	Janaki	F	27	20.6	154	98	32	119	NEGATIVE	0.57	0.61
3	Saroja	F	36	20.2	146	90	30	130	NEGATIVE	0.6	0.66
4	Prema	F	68	18.8	176	110	34	159	NEGATIVE	0.65	0.64
5	saran	M	32	19.9	163	98	36	145	NEGATIVE	0.7	0.59
6	Ganesh	M	55	20.4	160	103	28	141	>6	0.72	0.55
7	Paulraj	M	30	26.2	168	105	33	147	>6	0.74	0.61
8	Amuda	F	a	23.3	162	107	30	125	NEGATIVE	0.5	0.66
9	Allice	F	29	25.1	145	78	35	157	NEGATIVE	0.62	0.68
10	Javid	M	26	27	152	83	36	163	NEGATIVE	0.64	0.57
11	Vasantha	F	29	18.7	172	100	36	179	NEGATIVE	0.55	0.53
12	kannan	M	30	27.2	172	102	36	169	NEGATIVE	0.73	0.68
13	Kamala	F	17	18.6	152	99	28	125	NEGATIVE	0.58	0.61
14	Ponnamal	F	37	24.3	170	107	32	153	>6	0.71	0.52
15	Munuswamy	M	40	19	152	84	34	169	NEGATIVE	0.5	0.51
16	Jayalakshmi	F	54	22.4	158	97	35	128	NEGATIVE	0.61	0.57
17	Kalavathi	F	32	21.6	160	94	30	179	NEGATIVE	0.68	0.63
18	Komathi	F	24	22.8	144	91	24	143	NEGATIVE	0.56	0.68
19	subramani	M	22	20.2	166	100	36	149	NEGATIVE	0.53	0.59

20	Geethabai	F	48	19.4	142	84	26	160	NEGATIVE	0.59	0.64
21	Javeena	F	31	23.7	162	105	30	134	>6	0.75	0.78
22	kuppan	M	27	24.8	154	97	32	124	>6	0.51	0.72
23	Chokamal	F	60	19.9	146	90	30	126	NEGATIVE	0.57	0.73
24	Sangeetha	F	24	19	176	109	34	164	NEGATIVE	0.53	0.56
25	moses	M	24	22.9	163	99	36	140	>6	0.72	0.75
26	Rajeswari	F	23	23.4	160	102	28	146	NEGATIVE	0.64	0.52
27	Parimala	F	80	24.6	168	106	33	142	NEGATIVE	0.59	0.6
28	kaliammal	F	42	19.8	162	106	30	130	NEGATIVE	0.66	0.7
29	kumar	M	28	20.7	145	79	35	152	NEGATIVE	0.53	0.73
30	sundar	M	28	25.2	152	82	36	168	NEGATIVE	0.72	0.56
31	Saraswathi	F	24	18.9	172	101	36	174	>6	0.67	0.62
32	shankar	M	36	23.9	172	101	36	174	NEGATIVE	0.61	0.58
33	vijay	M	34	23.7	152	100	28	120	NEGATIVE	0.7	0.54
34	mohan	M	26	22.9	170	106	32	158	>6	0.72	0.56
35	Gandhimathi	F	18	25.7	152	85	34	164	NEGATIVE	0.6	0.59
36	Selvanayaki	F	28	26.2	158	96	35	132	NEGATIVE	0.54	0.52
37	Kasthuri	F	24	21.6	160	95	30	174	NEGATIVE	0.56	0.6
38	Sarasu	F	20	21.3	144	90	24	148	NEGATIVE	0.5	0.55
39	Gurunath	M	50	19.5	166	101	36	144	NEGATIVE	0.51	0.7
40	Priya	F	50	22.1	142	83	26	165	NEGATIVE	0.58	0.77

41	Rajesh	M	36	26.7	142	78	36	138	>6	0.52	0.76
42	Anjali	F	36	21	155	91	35	142	>6	0.56	0.77
43	Shankar	M	40	22.7	165	89	40	176		0.65	0.58
44	Krishnan	M	21	23.4	148	90	32	128	>6	0.72	0.65
45	Vimal	M	56	23.7	164	105	30	143	NEGATIVE	0.7	0.76
46	Thilaga	F	55	25.2	170	109	32	143	NEGATIVE	0.62	0.74
47	Jayaselan	M	42	27.6	152	88	28	118	NEGATIVE	0.56	0.69
48	Das	M	26	25.3	162	85	42	173	NEGATIVE	0.53	0.53
49	Elcy	F	28	18.9	162	92	35	174	NEGATIVE	0.67	0.61
50	Gunalakshmi	F	23	20.4	160	107	24	142	NEGATIVE	0.62	0.7
51	Munuswamy	M	20	23.7	166	84	30	138	NEGATIVE	0.56	0.63
52	Siva	M	30	26.4	158	90	33	164	>6	0.69	0.64
53	Rajinisha	F	52	21.3	168	99	32	126	>6	0.74	0.65
54	jagan	M	50	23	172	102	30	119	NEGATIVE	0.7	0.68
55	Indra	F	14	22.1	142	91	36	130	NEGATIVE	0.57	0.71
56	Malliga	F	30	24.3	164	85	34	140	NEGATIVE	0.63	0.54
57	Gowri	F	31	25.1	160	109	36	159	NEGATIVE	0.66	0.73
58	Rada	F	37	25.7	170	106	28	146	NEGATIVE	0.6	0.76
59	Nagalakshmi	F	35	27.2	166	101	32	145	NEGATIVE	0.57	0.63
60	Venila	F	14	19.4	154	105	30	142	NEGATIVE	0.6	0.66

61	Kanchana	F	28	18.9	145	105	36	141	>6	0.73	0.54
62	Rajina bee	F	29	22.8	176	107	35	130	NEGATIVE	0.65	0.52
63	Ramanan	M	14	24.6	170	100	36	147	NEGATIVE	0.61	0.57
64	Uma	F	18	26.9	163	90	24	152	NEGATIVE	0.52	0.56
65	Saroja	F	15	24.3	162	101	32	125	NEGATIVE	0.64	0.54
66	Saveetha	F	55	19.8	154	104	26	168	NEGATIVE	0.64	0.66
67	Narasiman	M	22	26.4	160	98	35	157	NEGATIVE	0.62	0.6
68	Valarmathi	F	14	19.8	142	84	35	174	NEGATIVE	0.54	0.51
69	Padma	F	23	23.3	176	90	24	163	NEGATIVE	0.72	0.74
70	Rosemary	F	26	23	164	107	32	174	NEGATIVE	0.69	0.65
71	Magesh	M	13	22.4	152	106	26	179	NEGATIVE	0.58	0.6
72	Guru	M	38	20.6	148	101	32	120	NEGATIVE	0.56	0.67
73	suresh	M	15	25.9	152	82	32	169	NEGATIVE	0.52	0.55
74	Saraswathi	F	13	27.1	160	110	42	158	NEGATIVE	0.63	0.64
75	Younis	M	36	23.4	152	100	34	125	NEGATIVE	0.66	0.61
76	mani	M	24	22.3	172	94	24	164	>6	0.68	0.58
77	Suguna	F	30	24.6	170	107	28	153	>6	0.73	0.72
78	Ragavan	M	30	20.6	152	109	28	132	>6	0.55	0.75

79	Salima	F	42	23.3	162	106	33	169		0.74	0.54
80	Parvathy	F	30	26.9	172	85	35	128	>6	0.64	0.52
81	Kousalya	F	26	19.6	144	78	34	174	>6	0.59	0.72
82	Mohan	M	29	22.8	154	89	36	179	NEGATIVE	0.55	0.74
83	Antony	M	16	24.8	160	78	30	148	NEGATIVE	0.51	0.62
84	Venkat	M	56	25.7	172	85	28	143	NEGATIVE	0.63	0.68
85	Chinnaponu	F	35	26.1	146	83	36	144	NEGATIVE	0.57	0.54
86	Jothy	F	22	20.9	170	92	34	149	NEGATIVE	0.55	0.64
87	Valli	F	12	18.7	165	99	36	165	NEGATIVE	0.52	0.73
88	Geetha	F	13	19.6	162	88	30	160	NEGATIVE	0.61	0.65
89	Shantha	F	22	22.7	158	91	40	134	>6	0.6	0.69
90	Murugan	M	40	26.2	162	83	30	138	NEGATIVE	0.58	0.55
91	Mayavathi	F	21	27.1	152	106	34	124	NEGATIVE	0.59	0.62
92	Meerajothi	F	16	20.4	162	79	36	142	NEGATIVE	0.54	0.6
93	Jayaram	M	32	23.3	146	90	30	143	NEGATIVE	0.75	0.52
94	Raja	M	18	19.3	144	96	30	176	NEGATIVE	0.71	0.57
95	shanthakumar	M	13	26.6	142	98	35	118	>6	0.69	0.58
96	arokiaswamy	M	12	18.8	155	92	36	128	NEGATIVE	0.67	0.52
97	Hemath	M	28	20.9	162	97	36	173	NEGATIVE	0.65	0.56
98	senthil	M	12	21.6	168	107	35	143	NEGATIVE	0.62	0.67
99	muthu	M	16	22	145	100	30	174	NEGATIVE	0.61	0.54

100	velu	M	45	22.7	152	98	36	142	NEGATIVE	0.56	0.58

							PHENYTOIN									
S.NO.	**NAME**	**AGE (years)**	**SEX**	**MIN NO**	**DURATION**	**DOSAGE mg**	**seizure type**	**Etioloy**	**BMI kg/m2**	**TC mg%**	**LDL mg%**	**HDL mg%**	**TGL mg%**	**CRP mg/L**	**IMT(R)mmIMT(L) mm**	**IMT (LT)**
1	Veerammal	40	F	16615/11	2 years	300	GTCS	Idiopathic	23.3	152	106	30	139	NEGATIVE	0.53	0.83
2	Yasmin	28	F	14842/11	2	300	GTCS	Idiopathic	24.4	155	99	32	119	NEGATIVE	0.56	0.86
3	Kuppu	38	F	14834/11	2	200	GTCS	Idiopathic	20.2	150	95	29	130	NEGATIVE	0.65	0.76
4	Arumugam	70	M	83467/10	3	300	GTCS	Idiopathic	20.9	166	92	29	159	>6	1.03	0.78
5	Ramani	34	F	26582/08	9	300	GTCS	Idiopathic	21.6	157	89	34	145	>6	0.98	0.6
6	Chandran	53	M	12428/03	4	200	GTCS	Idiopathic	23.9	162	90	35	141	NEGATIVE	0.62	0.82
7	Subbulaxmi	29	F	4494/10	2	200	GTCS	Idiopathic	23.2	170	88	33	147	NEGATIVE	0.54	0.64
8	Annapoorna	40	F	1332/10	8	200	GTCS	Idiopathic	23.4	154	99	31	125	>6	1.04	0.71
9	subbulaxmi	29	F	4494/10	5	300	GTCS	Idiopathic	25.5	159	93	39	157	>6	0.85	0.63
10	velmurugan	26	M	32939/07	2	200	GTCS	Idiopathic	26	164	89	30	163	NEGATIVE	0.51	0.8
11	vembu	28	F	3206/05	7	300	GTCS	symptomatic	29.4	151	92	32	179	>6	0.77	0.61
12	saravanan	30	M	34841/08	4	300	GTCS	Idiopathic	29.1	154	100	37	169	>6	0.73	0.66
13	subash	16	M	2653/10	3	200	GTCS	Idiopathic	29.9	150	102	32	125	NEGATIVE	0.6	0.88
14	CHARLES	37	M	16533/09	15	200	GTCS	Symptomatic	32.1	155	107	30	153	>6	0.99	0.7
15	Kanniga	42	F	21151/02	10	300	GTCS	Idiopathic	31.1	157	103	37	169	NEGATIVE	0.81	0.66
16	Parameshwaran	55	M	30749/98	15	300	GTCS	symptomatic	28.4	159	96	36	128	>6	0.89	0.78
17	Ganesan	31	M	21541/03	9	300	GTCS	Idiopathic	30.3	150	89	34	179	NEGATIVE	0.73	0.74
18	Leelavathy	23	F	19181/10	2	200	CPS	Idiopathic	27.6	152	91	32	143	NEGATIVE	0.58	0.62
19	Rajesh	21	M	791/10	2	200	GTCS	Idiopathic	26.7	151	94	35	149	NEGATIVE	0.64	0.8
20	Usha	49	F	14152/08	4	300	Partial	Idiopathic	25.5	155	96	37	160	NEGATIVE	0.55	0.6
21	kumaravel	30	M	33955/08	4	300	GTCS	Idiopathic	26	157	98	37	134	>6	1.01	0.76
22	Mythili	27	F	30560/10	2	200	GTCS	Idiopathic	24.4	159	104	34	124	>6	0.93	0.72
23	JAYALAXMI	61	F	21848/09	10	300	GTCS	Idiopathic	22.8	161	108	31	126	>6	0.91	0.92
24	Bagyalakshmi	25	F	21127/08	4	200	GTCS	Symptomatic	22.7	160	100	35	164	>6	0.84	0.9
25	Akbar	24	M	453/05	7	400	GTCS	Idiopathic	20.4	161	106	38	140	>6	0.86	0.95
26	Balachandar	23	M	12862/02	4	300	GTCS	Idiopathic	21	151	96	37	146	NEGATIVE	0.67	0.77
27	Barani	82	F	27036/10	2	200	GTCS	Idiopathic	29.3	163	94	35	142	>6	0.68	0.84
28	govindasamy	44	M	12047/08	4	300	GTCS	Idiopathic	31.6	154	89	30	130	>6	0.59	0.58
29	pachaiyappan	28	M	23454/08	5	200	GTCS	Idiopathic	32.3	164	92	33	152	>6	0.97	0.6
30	SATHYA	24	F	1361/07	4	300	GTCS	Idiopathic	30.7	157	97	32	168	>6	0.75	0.79
31	David	38	M	21621/09	3	200	GTCS	Idiopathic	28.9	169	98	36	174	>6	0.72	0.67
32	suresh	35	M	29431/08	4	200	GTCS	Idiopathic	27.1	160	102	38	162	NEGATIVE	0.61	0.73

CARBAMAZEPINE																
33	Shobana	27	F	53041/02	10	400	GTCS	Idiopathic	23	154	89	30	154	NEGATIVE	0.57	0.53
34	Karthika	17	F	52143/02	10	400	Partial	symptomatic	22.2	168	97	36	155	>6	0.63	0.59
35	BALAJI	29	M	2201/94	8	400	GTCS	Idiopathic	27.4	188	122	32	159	>6	0.87	0.65
36	KANNAGI	24	F	2816/07	7	1200	GTCS	Idiopathic	19.1	196	130	30	160	>6	0.83	0.91
37	AMSAVALLI	22	F	5382/10	3	400	Partial	symptomatic	18.8	142	83	22	148	NEGATIVE	0.56	0.84
38	Karthik	52	M	21193/06	6	400	GTCS	symptomatic	24.4	172	104	34	159	NEGATIVE	0.48	0.82
39	VASANTHA	50	F	14703/04	8	400	GTCS	Idiopathic	22.4	182	114	32	150	NEGATIVE	0.59	0.74
40	SRINIVASAN	38	M	4275/10	2	400	GTCS	Idiopathic	25.1	174	106	37	154	NEGATIVE	0.65	0.72
41	RAJAVENI	38	F	27074/97	15	800	Partial	Idiopathic	20.9	176	106	36	137	>6	0.89	0.51
42	Parameshwaran	40	M	5120/94	10	600	GTCS	Idiopathic	21.5	182	122	26	144	>6	0.78	0.83
43	VIMALA	21	F	15232/96	10	600	CPS	Idiopathic	25.7	170	107	28	141	>6	0.74	0.92
44	RAVI	57	M	18694/94	18	600	GTCS	Idiopathic	24.2	192	126	32	160	>6	0.71	0.66
45	SOUNDARAJAN	60	M	36817/06	6	600	CPS	Idiopathic	22.8	152	91	30	155	NEGATIVE	0.61	0.69
46	SRILATHA	43	F	16881/04	8	600	GTCS	Idiopathic	22.2	184	129	26	141	>6	0.83	0.77
47	REVATHI	25	F	170871/98	12	400	Partial	symptomatic	24.4	182	111	37	132	>6	0.88	0.79
48	SASIKALA	28	F	4201/98	14	400	GTCS	Idiopathic	23.6	184	109	43	159	>6	0.76	0.53
49	ABDUL VASI	23	M	5062/09	3	400	CPS	Idiopathic	22.6	174	106	33	133	NEGATIVE	0.49	0.57
50	YASODHA	32	F	26299/05	8	800	GTCS	Idiopathic	24.4	146	74	40	159	>6	0.82	0.64
51	KANNIYAPPAN	54	M	21517/01	11	600	CPS	Idiopathic	24.1	208	139	34	165	>6	0.75	0.68
52	MURUAN	53	M	33720/07	5	400	GTCS	Idiopathic	26.6	168	106	30	157	>6	0.71	0.82
53	ASHWINI	14	F	23643/07	5	400	GTCS	Idiopathic	26.7	154	89	30	172	>6	0.7	0.86
54	JAYALAXMI	30	F	83542/07	5	400	GTCS	Idiopathic	20.8	168	96	36	178	NEGATIVE	0.57	0.74
55	DHANALAKSHMI	40	F	124662/90	10	600	Partial	Idiopathic	21.6	188	123	32	164	NEGATIVE	0.52	0.53
56	BAKIYAM	37	F	3238/09	3	400	GTCS	Idiopathic	26.5	196	129	30	154	NEGATIVE	0.64	0.64
57	SHANTI	36	F	6577/90	20	600	GTCS	Idiopathic	22.2	142	84	22	158	>6	0.88	0.67
58	ANITHA	14	F	31386/10	3	400	Partial	Idiopathic	23.6	172	103	34	164	>6	0.74	0.76
59	ABDUL WAHID	30	M	32326/05	7	400	GTCS	Idiopathic	22.9	182	115	32	142	NEGATIVE	0.66	0.9
60	ABDUL RASAK	29	M	5127/05	7	400	GTCS	Idiopathic	22.4	174	105	37	160	NEGATIVE	0.5	0.84

SODIUM VALPROATE																
61	SARANYAN	14	M	3177/07	6	500	GTCS	Idiopathic	29.5	162	92	34	156	NEGATIVE	0.65	0.62
62	SATHISH	16	M	37200/09	3	400	GTCS	Idiopathic	19.2	165	104	29	134	NEGATIVE	0.72	0.68
63	SANGEETHA	14	F	3729/04	8	600	GTCS	Idiopathic	20.8	153	89	38	162	NEGATIVE	0.8	0.58
64	PENCILLAMA	60	F	34837/08	10	600	GTCS	symptomatic	24.3	151	90	33	167	>6	0.87	0.82
65	JAQUALINE	20	F	25443/10	2	400	GTCS	Idiopathic	22.8	160	106	32	172	NEGATIVE	0.57	0.75
66	SARAVANAN	16	M	13265/10	3	400	GTCS	Idiopathic	26.8	166	107	29	164	>6	0.88	0.73
67	SWATHI	25	F	12044/02	4	600	GTCS	symptomatic	22.7	169	97	33	167	NEGATIVE	0.61	0.6
68	MOHANASUNDARI	29	F	32132/11	2	600	GTCS	Idiopathic	20.1	154	99	39	153	NEGATIVE	0.69	0.83
69	ABILASH	13	M	25658/10	2	400	GTCS	Idiopathic	19.2	152	102	35	152	NEGATIVE	0.56	0.62
70	BALASUBRAMANIAM	53	M	16239/98	12	1600	GTCS	Idiopathic	26.5	150	107	34	159	>6	0.85	0.7
71	ARUN KUMAR	15	M	25621/03	9	400	GTCS	Idiopathic	28.8	159	104	33	130	NEGATIVE	0.67	0.74
72	Arumugam	12	M	8645/06	6	400	GTCS	Idiopathic	27.9	160	93	36	154	NEGATIVE	0.77	0.66
73	ARULRAJ	38	M	36087/07	11	400	GTCS	Idiopathic	27.4	161	91	38	136	>6	0.84	0.58
74	JENNIE	24	F	25446/03	4	400	GTCS	Idiopathic	23.6	163	90	32	155	NEGATIVE	0.63	0.67
75	ANSAR BASHA	30	M	36943/07	5	600	GTCS	Idiopathic	20	162	94	29	161	NEGATIVE	0.59	0.63
76	ANNADURAI	32	M	23235/03	8	600	GTCS	Idiopathic	19.1	165	101	39	167	>6	0.83	0.75
77	ANAND	44	M	6750/05	10	600	GTCS	Idiopathic	23.3	168	104	37	155	NEGATIVE	0.71	0.79
78	BASKAR	34	M	3586/99	5	400	GTCS	Idiopathic	24.1	154	107	36	165	NEGATIVE	0.64	0.81
79	ANSAR BEE	24	F	1849/98	10	600	MYOCLONUS	Idiopathic	25.2	152	96	33	142	NEGATIVE	0.71	0.6
80	ANTHONY AMMAL	28	F	37277/08	9	800	GTCS	Idiopathic	26.1	153	94	31	130	>6	0.85	0.7
81	ARUN	17	M	20672/98	6	400	Partial	Idiopathic	28.6	156	99	34	154	NEGATIVE	0.59	0.68
PHENOBARBITONE																
82	BABY	58	F	6301/80	11	30	GTCS	Idiopathic	18.7	176	107	36	142	>6	0.86	0.72
83	BALAKUMAR	35	M	1310/03	8	60	GTCS	Idiopathic	24.6	182	121	26	154	NEGATIVE	0.65	0.59
84	CHANDRAKALA	12	F	6059/03	8	60	GTCS	Idiopathic	24.2	170	108	28	160	NEGATIVE	0.55	0.54
85	MANIKANDAN	13	M	22422/09	20	30	GTCS	Idiopathic	22.1	192	125	32	162	>6	0.84	0.78
86	BHAVANI	21	F	5018/01	9	60	GTCS	Idiopathic	27	152	92	30	150	NEGATIVE	0.53	0.69
87	REKHA	43	F	10308/90	4	30	Partial	Idiopathic	20.2	184	128	26	146	NEGATIVE	0.62	0.8
88	BHASKARAN	28	M	12668/98	4	30	GTCS	Idiopathic	20.8	182	112	37	144	NEGATIVE	0.67	0.61

89	ELIYAS	17	M	36550/99	11	60	GTCS	Idiopathic	19.4	184	108	43	144	NEGATIVE	0.72	0.56
90	LATHA	33	F	3775/06	7	30	GTCS	Idiopathic	22.8	174	107	33	148	NEGATIVE	0.77	0.66
91	KISHORE	18	M	12086/03	9	30	GTCS	symptomatic	20.8	146	73	40	134	>6	0.82	0.76
92	BHAVANI	13	F	27638/08	12	60	GTCS	Idiopathic	18.6	208	140	34	150	>6	0.87	0.74
93	KAVIRAMAN	10	M	28252/06	6	45	GTCS	Idiopathic	18.4	168	105	30	162	NEGATIVE	0.54	0.68
94	BHASKAR	26	M	3789/89	4	60	GTCS	Idiopathic	19.4	148	71	44	164	NEGATIVE	0.63	0.57
95	HEMALATHA	13	F	17805/07	5	60	GTCS	symptomatic	21.2	184	120	28	160	NEGATIVE	0.69	0.7
96	HAZEERA	13	F	16137/02	10	30	GTCS	Idiopathic	21.9	152	89	26	182	NEGATIVE	0.74	0.78
97	BHANUMATHI	45	F	12629/95	10	60	GTCS	Idiopathic	24.4	164	87	42	154	>6	0.85	0.71
98	DHANALAKSHMI	43	F	9145/89	8	60	GTCS	Idiopathic	21.5	198	141	30	132	NEGATIVE	0.78	0.6
99	KAIRUN NISHA	33	F	6637/99	11	15	GTCS	Idiopathic	22.8	170	109	35	130	NEGATIVE	0.76	0.64
100	DHANALAKSHMI	13	F	24734/11	2	60	GTCS	Idiopathic	22.4	174	107	32	154	NEGATIVE	0.65	0.55